

WO0242326

Publication Title:

Method of expression and agents identified thereby

Abstract:

The present invention relates generally to a method for the in vitro or in vivo production, by a eukaryotic host cell, of a protein from a negative sense single stranded RNA virus and, more particularly, to a method for the in vitro or in vivo production by a eukaryotic host cell of a protein from a virus of the family Paramyxoviridae and agents identified thereby. Still more particularly, said protein is the F, N, P or SH protein, the encoding nucleic acid molecule of which has been optimised for expression in a eukaryotic host cell. In yet another aspect, the present invention relates to a method for modulating the functional activity of an F protein. More particularly, said modulation is predicated on modulation of the functioning of a novel intrasequence cleavage event. In still another aspect, the protein expression product produced in accordance with the optimised expression method of the present invention and the method of modulating F protein functional activity are useful in a range of applications including, but not limited to, the identification, design and/or modification of agents capable of modulating functional activity of the subject protein. The proteins, encoding nucleic acid molecules and agents identified in accordance with the present invention are useful, inter alia, in the treatment and/or prophylaxis of viral infections.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 May 2002 (30.05.2002)

PCT

(10) International Publication Number
WO 02/42326 A1

(51) International Patent Classification⁷: C07K 14/08, 14/115, 14/135, 16/10, A61K 38/16, 39/155, A61P 11/00, C12N 15/45, 15/40, C12Q 1/68, G01N 1/68

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(21) International Application Number: PCT/AU01/01517

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,

(22) International Filing Date:
22 November 2001 (22.11.2001)

AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/252,767 22 November 2000 (22.11.2000) US

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: A METHOD OF EXPRESSION AND AGENTS IDENTIFIED THEREBY

(57) **Abstract:** The present invention relates generally to a method for the *in vitro* or *in vivo* production, by a eukaryotic host cell, of a protein from a negative sense single stranded RNA virus and, more particularly, to a method for the *in vitro* or *in vivo* production by a eukaryotic host cell of a protein from a virus of the family Paramyxoviridae and agents identified thereby. Still more particularly, said protein is the F, N, P or SH protein, the encoding nucleic acid molecule of which has been optimised for expression in a eukaryotic host cell. In yet another aspect, the present invention relates to a method for modulating the functional activity of an F protein. More particularly, said modulation is predicated on modulation of the functioning of a novel intrasequence cleavage event. In still another aspect, the protein expression product produced in accordance with the optimised expression method of the present invention and the method of modulating F protein functional activity are useful in a range of applications including, but not limited to, the identification, design and/or modification of agents capable of modulating functional activity of the subject protein. The proteins, encoding nucleic acid molecules and agents identified in accordance with the present invention are useful, *inter alia*, in the treatment and/or prophylaxis of viral infections.

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A METHOD OF EXPRESSION AND AGENTS IDENTIFIED THEREBY

FIELD OF THE INVENTION

5 The present invention relates generally to a method for the *in vitro* or *in vivo* production, by a eukaryotic host cell, of a protein from a negative sense single stranded RNA virus and, more particularly, to a method for the *in vitro* or *in vivo* production by a eukaryotic host cell of a protein from a virus of the family Paramyxoviridae and agents identified thereby. Still more particularly, said protein is the F, N, P or SH protein, the encoding
10 nucleic acid molecule of which has been optimised for expression in a eukaryotic host cell. In yet another aspect, the present invention relates to a method for modulating the functional activity of an F protein. More particularly, said modulation is predicated on modulation of the functioning of a novel intrasequence cleavage event. In still another aspect, the protein expression product produced in accordance with the optimised
15 expression method of the present invention and the method of modulating F protein functional activity are useful in a range of applications including, but not limited to, the identification, design and/or modification of agents capable of modulating functional activity of the subject protein. The proteins, encoding nucleic acid molecules and agents identified in accordance with the present invention are useful, *inter alia*, in the treatment
20 and/or prophylaxis of viral infections.

BACKGROUND OF THE INVENTION

Bibliographic details of the publications referred to by author in this specification are
25 collected alphabetically at the end of the description.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

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Paramyxoviridae describes a family of enveloped viruses which exhibit a non-segmented, negative sense single stranded RNA genome. This family includes some significant pathogens of humans, animals and birds including the causal agents of measles, mumps, Newcastle disease, various respiratory diseases, Rinderpest and canine distemper.

5

Within this family exist two subfamilies (Paramyxovirinae and Pneumovirinae). Each subfamily comprises a number of genera - the genera of Pneumovirinae being Pneumovirus. In general, infection by these viruses occurs by fusion of the virus envelope with the plasma membrane of the host cell. Transcription and replication occur in the 10 cytoplasm. Virions mature by budding through the host cell plasma membrane at sites containing the virus envelope proteins. Infected host cells commonly lyse, but temperate and persistent infections also occur. Infection of the host cell commonly results in cell fusion and syncytium formation, inclusions and haemadsorption.

15 The Pneumovirus genus of Paramyxoviridae differ from Rubulavirus, Morbillivirus and Paramyxovirus genera in that the members lack both haemagglutinin and neuraminidase activity. The Pneumovirus genus includes bovine and human respiratory syncytial virus amongst others. The latter virus is known to cause severe respiratory disease of humans whereas the former is an example of a family member responsible for animal diseases.

20

In general terms, the Paramyxovirus virion consists of a helical nucleocapsid, composed of genomic single stranded RNA and proteins NP, P and L, surrounded by an envelope containing a non-glycosylated M protein in the inner layer and two glycoproteins which extend across the width of the envelope and beyond the outer surface to form spikes. The 25 larger of the envelope glycoproteins (often designated HN) exhibits cell binding, haemagglutinating and neuraminidase activities, while the smaller F (fusion) protein often exhibits haemolytic activity and promotes fusion between the virus envelope and the host plasma membrane. The F protein can also promote cell-cell fusion. The F protein is generally synthesised as an inactive precursor which is activated by proteolytic cleavage. 30 In Pneumoviruses the G glycoprotein substitutes for HN.

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Host cell infection is thought to occur by adsorption, via HN or G, to the cell surface, followed by F protein mediated fusion between the virus envelope and the host plasma membrane. Viral glycoproteins are also synthesised on membrane bound polysomes, glycosylated, and inserted into the host plasma membrane. During maturation, the virions
5 bud through the region of the membrane containing these proteins. Accordingly, in terms of treating Paramyxoviridae virus infectivity, modulation of F protein functional activity provides a potential therapeutic mechanism since down-regulating or inhibiting F protein functioning would interfere with F protein mediated fusion of the virion with a potential host cell, and/or virion budding from cells which are already infected. However, in order
10 to screen for agents which can modulate F protein functional activity, or to utilise F protein for any other purpose, it is necessary to establish an efficient and routinely reproducible *in vitro* system of producing recombinant F proteins, and in particular functionally active F proteins. To date this has proved elusive with existing expression systems producing only low levels of either inactive or very poorly active F proteins which often require co-
15 expression with other viral glycoproteins to form syncytia. Further, to the extent that F protein is produced, albeit inactive or poorly active, only very low concentrations of protein products have been obtained.

The notion of codon usage is a poorly understood phenomenon which impacts on the
20 efficiency of expression product production by given cells. Specifically, it has been determined that the levels of expression of protein produced by a cell can vary depending on the particular form of codon which is expressed in relation to a given amino acid. Although some amino acids are encoded by only one type of codon, other amino acids are encoded by up to six different codons, the efficiency of expression of which will vary
25 depending on the host cell in which it is being expressed. It appears that certain types of cells exhibits preferences for expressing certain codon forms.

In work leading up to the present invention, the inventors have developed an *in vitro* expression system which both facilitates the production of functionally active F protein
30 expression product and facilitate the production of significantly higher concentrations of F protein, or fragments thereof, than has been previously available. This system is based on

identification by the inventors of two aspects of negative sense single stranded RNA viral protein expression which are compromised when the subject expression is performed in eukaryotic cells *in vitro*, these being inefficient codon usage and the presence of unwanted intrasequence mRNA splice sites.

5

- With respect to the former aspect, the inventors have identified codons within the viral protein nucleic acid encoding molecule which are not efficiently expressed by a given eukaryotic host cell due to their not taking a form preferred by the host cell of interest. By establishing the form of codon preferably expressed by a given host cell, and modifying 10 the viral protein encoding DNA sequence accordingly, the inventors have achieved levels of viral protein production, in particular F protein production, which have not, to date, been obtainable in normal mammalian expression systems. Further, the method of the present invention facilitates the production of functionally active F proteins.
- 15 In light of the fact that the basis and mechanism of codon usage preferences are not fully understood, there exist no conclusive theoretical principals by which one can predict with any certainty precisely which codons are not preferred by a given host cell nor which form they should ideally take. Accordingly, the successful development of viral protein encoding nucleic acid molecules which exhibits codons preferred by eukaryotic cells is a 20 significant development.

With respect to the latter aspect of *in vitro* expression of the subject viral proteins, the inventors have further surprisingly determined that the *in vitro* expression of negative sense single stranded RNA viral proteins is compromised where *in vitro* expression is 25 based on expression of a complementary DNA form of the naturally occurring RNA sequence encoding the protein of interest. This is due in part to the unexpected presence of RNA splice sites. Identification and removal of the unwanted splice sites has further facilitated efficient and increased viral protein production.

- 30 In a related aspect, and with respect to the F protein in particular, the inventors have identified a previously unknown intrasequence cleavage site which is involved in the

generation of functionally active F protein. Identification of this cleavage site now facilitates, *inter alia*, development of methods and identification of agents for modulation F protein cleavage and thereby methods of modulating F protein functioning.

- 5 The developments herein described now permit the identification and/or rational analysis, design and/or modification of agents for use in modulating viral protein functional activity and, in particular, F protein functional activity. Further, the developments of the present invention also facilitate generation of DNA and protein vaccines directed to the *in vivo* induction of an immune response to the subject proteins. The viral molecules produced in
10 accordance with the method of the present invention and agents herein identified are useful *inter alia*, in a range of prophylactic and therapeutic applications relating to viral infections.

SUMMARY OF THE INVENTION

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Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

20

The subject specification contains nucleotide and amino acid sequence information prepared using the programme PatentIn Version 3.1, presented herein after the bibliography. Each nucleotide or amino acid sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (e.g. <210>1, <210>2, etc). The length, type of sequence (DNA, protein (PRT), etc) and source of organism for each nucleotide or amino acid sequence are indicated by information provided in the numeric indicator fields <211>, <212> and <213>, respectively. Nucleotide and amino acid sequences referred to in the specification are defined in the information provided in numeric indicator field <400> followed by the sequence identifier (e.g. <400>1, <400>2, etc). A summary of the sequence listings herein provided is detailed in Table 1.

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Specific mutations in amino acid sequence are represented herein as "Xaa₁nXaa₂" where Xaa₁ is the original amino acid residue before mutation, n is the residue number and Xaa₂ is the mutant amino acid. The abbreviation "Xaa" may be the three letter or single letter amino acid code. A mutation in single letter code is represented, for example, by X₁nX₂ 5 where X₁ and X₂ are the same as Xaa₁ and Xaa₂, respectively. The amino acid residues for F protein are numbered with the first residue R in the motif RARR being residue number 106.

One aspect of the present invention is directed to a method of facilitating production of a 10 protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a host cell a nucleic acid molecule encoding said protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by a eukaryotic cell.

15 Another aspect of the present invention provides a method of facilitating production of a protein or derivative thereof from a virus of the family Paramyxoviridae, said method comprising expressing in a host cell a nucleic acid molecule encoding said protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by a eukaryotic host cell.

20 Yet another aspect of the present invention provides a method of facilitating production of a protein or derivative thereof from a negative sense single stranded RNA virus, which protein directly or indirectly facilitates fusion of any one or more viral components with any one or more host cell components, said method comprising expressing in a host cell a 25 nucleic acid molecule encoding said protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by a eukaryotic cell.

Still another aspect of the present invention is therefore more particularly directed to a 30 method of facilitating production of a F protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a host cell a nucleic acid

molecule encoding said F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by a eukaryotic cell.

Yet still another aspect of the present invention provides a method of facilitating
5 production of a N protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a host cell a nucleic acid molecule encoding said N protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by a eukaryotic cell.

10 Still yet another aspect of the present invention provides a method of facilitating production of a P protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a host cell a nucleic acid molecule encoding said P protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by a eukaryotic cell.

15 A further aspect provides a method of facilitating production of a SH protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a host cell a nucleic acid molecule encoding said SH protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for
20 expression by a eukaryotic cell.

Another further aspect provides a method of facilitating production of a protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said
25 protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell.

Yet another further aspect of the present invention is directed to a method of facilitating production of a protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said protein or derivative thereof, the nucleotide sequence of which
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nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is codon optimisation and/or nucleotide splice site deletion.

Still another further aspect provides a method of facilitating production of F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is nucleotide splice site deletion.

10 Still yet another further aspect of the present invention is directed to a method of facilitating production of a F_{sol} portion of an F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a host cell a nucleic acid molecule encoding said F_{sol} portion or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein
15 said optimisation is nucleotide splice site deletion.

Yet still another further aspect provides a method of facilitating production of F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is codon optimisation.

Another aspect of the present invention is directed to a method of facilitating production of a F_{sol} portion of an F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a host cell a nucleic acid molecule encoding said F_{sol} portion or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is codon optimisation.

30 Yet another aspect of the present invention provides a method of facilitating production of F protein or derivative thereof from respiratory syncytial virus, said method comprising

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expressing in a mammalian host cell a nucleic acid molecule encoding said F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is nucleotide splice site deletion and codon optimisation.

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Still another another aspect of the present invention provides a method of facilitating the production of a F protein or derivative thereof from a respiratory syncytial virus, said method comprising expressing in a host cell the nucleotide sequence set forth in <400>5 or derivative thereof.

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Yet still another aspect provides a method of facilitating the production of a F_{sol} portion of an F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a host cell the nucleotide sequence set forth in <400>6 or derivative thereof.

15

Still yet another aspect provides a method of facilitating production of P protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said P protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is codon optimisation.

20

A further aspect provides a method of facilitating the production of a P protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a host cell the nucleotide sequence set forth in <400>556 or derivative thereof.

25

Another further aspect provides a method of facilitating production of N protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said N protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is codon optimisation.

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- 10 -

Yet another further aspect provides a method of facilitating the production of a N protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a host cell the nucleotide sequence set forth in <400>559 or derivative thereof.

- 5 Still another further aspect provides a method of facilitating production of SH protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said SH protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is codon optimisation.

10

Still yet another further aspect provides a method of facilitating the production of a SH protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a host cell the nucleotide sequence set forth in <400>562 or derivative thereof.

15

In another aspect, the present invention should be understood to extend to the optimised nucleic acid molecules described herein and to the expression products derived therefrom.

- 20 Yet another aspect of the present invention is directed to a method of regulating the functional activity of a viral F protein, which protein in its non-fully functional form comprises an F2 portion linked, bound or otherwise associated with an F1 portion, which F2 portion comprises an intervening peptide sequence, said method comprising modulating cleavage of said intervening peptide sequence wherein excision of at least part of said intervening sequence from said non-fully functional form of said F protein up-regulates F
- 25 protein functional activity.

- 30 Still another aspect of the present invention is directed to a method of regulating the functional activity of a Paramyxoviridae derived F protein, which protein in its non-fully functional form comprises an F2 portion linked, bound or otherwise associated with an F1 portion, which F2 portion comprises an intervening peptide sequence, said method comprising modulating cleavage of said intervening peptide sequence wherein excision of

at least part of said intervening sequence from said non-fully functional form of said F protein up-regulates F protein functional activity.

Yet still another aspect of the present invention provides a method of regulating the 5 functional activity of a respiratory syncytial virus F protein, which protein in its non-fully functional form comprises an F2 portion linked, bound or otherwise associated with an F1 portion, which F2 portion comprises an intervening peptide sequence, said method comprising modulating cleavage of said intervening peptide sequence, wherein excision of at least part of said intervening sequence from said non-fully functional form of said F 10 protein up-regulates F protein functional activity and wherein said cleavage events occur at the cleavage sites defined by the peptide sequences RARR (<400>564) and KKRKRR (<400>563).

In a related aspect, the present invention provides a method of regulating the functional 15 activity of a viral F protein, which protein in its non-fully functional form comprises the structure:

X₁, X₂, X₃

20 wherein:

X₁ comprises the non-intervening peptide sequence region of the F2 portion;

X₂ comprises the intervening peptide sequence region of the F₂ portion; and

X₃ comprises the F1 portion

25 said method comprising modulating cleavage of said intervening peptide sequence wherein excision of at least part of said intervening sequence from said non-fully functional form of said F protein up-regulates F protein functional activity.

Still yet another aspect provides a method of inhibiting, retarding or otherwise down- 30 regulating the functional activity of a Paramyxoviridae derived F protein, which protein in its non-fully functional form comprises an F2 portion linked, bound or otherwise

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associated with an F1 portion, which F2 portion comprises an intervening peptide sequence, said method comprising inhibiting or otherwise down-regulating cleavage of said intervening peptide sequence.

- 5 A further aspect of the present invention provides a method of down-regulating the functional activity of a Paramyxoviridae derived F protein, which protein in its non-fully functional form comprises the structure:

X₁X₂X₃

10

wherein:

X₁ comprises the non-intervening peptide sequence region of the F2 portion;
X₂ comprises the intervening peptide sequence region of the F2 portion; and
X₃ comprises the F1 portion

15

said method comprising inhibiting or otherwise down-regulating cleavage of said intervening peptide sequence.

- Another further aspect provides a method for detecting an agent capable of regulating the
20 functional activity of a viral F protein or derivative thereof said method comprising
contacting a eukaryotic cell expressing an optimised nucleic acid molecule encoding said
viral F protein or derivative thereof, as hereinbefore described, with a putative modulatory
agent and detecting an altered expression phenotype and/or functional activity.

- 25 In yet another aspect there is provided a method for detecting an agent capable of
regulating the functional activity of a viral F protein or derivative thereof said method
comprising contacting a host cell, which host cell expresses a nucleic acid molecule
encoding the non-fully functional form of said viral F protein or derivative thereof as
hereinbefore described, with a putative modulatory agent and detecting an altered
30 expression phenotype and/or altered functional activity wherein said agent modulates
cleavage of the intervening peptide sequence.

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Still another further aspect of the present invention is directed to a method for analysing, designing and/or modifying an agent capable of interacting with a viral F protein or derivative thereof and modulating at least one functional activity associated with said 5 protein, which protein is produced in accordance with the method of the present invention said method comprising contacting said F protein or derivative thereof with a putative agent and assessing the degree of interactive complementarity of said agent with said protein.

Still yet another further aspect of the present invention is directed to an agent capable of 10 interacting with a viral F protein and modulating at least one functional activity associated with said viral protein.

In still another aspect there is provided a viral F protein variant comprising a mutation in the intervening peptide sequence wherein said variant exhibits modulated functional 15 activity relative to wild type F protein or a derivative, homologue, analogue, chemical equivalent or mimetic of said variant.

Another aspect of the present invention provides a viral F protein variant comprising a mutation in the intervening peptide sequence wherein said variant exhibits down-regulated 20 functional activity relative to wild type F protein or a derivative, homologue, analogue, chemical equivalent or mimetic of said variant.

Yet another aspect provides a respiratory syncytial virus F protein variant comprising a mutation in the cleavage site defined by amino acids RARR (<400>564) wherein said 25 variant exhibits down-regulated functional activity relative to wild type F protein or a derivative, homologue, analogue, chemical equivalent or mimetic of said variant.

Preferably said mutation comprises one or more of the amino acid substitutions selected from the following list:

30

(i) R106G

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- (ii) A107Q
- (iii) R108G

Still more preferably said F protein variant comprises the sequence substantially as set
5 forth in <400>565.

Still another aspect provides a respiratory syncytial virus F protein variant comprising a
multiple amino acid deletion from the intervening peptide sequence wherein said variant
exhibits down-regulated functional activity relative to wild type F protein or a derivative,
10 homologue, analogue, chemical equivalent of said variant.

It is more preferably provided that said amino acid deletion is a partial deletion of the
intervening peptide sequence and more preferably a deletion of the peptide sequence

15 RARRELPRFMNYTLNNAKKTNVTLS <400>569.

Still more preferably said variant comprises the amino acid sequence substantially as set
forth in <400>567.

20 Yet still another aspect of the present invention is directed to an isolated nucleic acid
molecule selected from the list consisting of:

- (i) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a
nucleotide sequence encoding or complementary to a sequence encoding a viral F
protein variant or derivative, homologue, analogue, chemical equivalent or mimetic
25 of said variant, which variant comprises a mutation in the intervening peptide
sequence wherein said variant exhibits modulated functional activity relative to
wild-type F protein.
- (ii) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a
nucleotide sequence encoding or complementary to a sequence encoding a viral F
protein variant or derivative, homologue, analogue, chemical equivalent or mimetic
30

- 15 -

of said variant, which variant comprises a mutation in the intervening peptide sequence wherein said variant exhibits down-regulated functional activity relative to wild-type F protein.

5 (iii) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a respiratory syncytial virus F protein or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a mutation in the cleavage site defined by amino acids RARR wherein said variant exhibits down-
10 regulated functional activity relative to wild-type F protein.

(iv) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a respiratory syncytial virus F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises one or
15 more of the amino acid substitutions selected from the following list:

- (a) R106G
- (b) A107Q
- (c) R108G

20 (v) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a multiple amino acid deletion from the intervening peptide sequence wherein said variant exhibits down-regulated
25 functional activity relative to wild-type F protein.

30 (vi) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic

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of said variant, which variant comprises a partial deletion of the intervening peptide sequence and more preferably a deletion of the peptide sequence

RARRELPRFMNYTLNNAKKTNVTLS <400>569.

5

(vii) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises the amino acid sequence substantially as set forth in <400>567.

10

(viii) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises the amino acid sequence substantially as set forth in <400>565.

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(ix) An isolated nucleic acid molecule or derivative or analogue thereof comprising the nucleotide substantially as set forth in <400>568.

20

(x) An isolated nucleic acid molecule or derivative or analogue thereof comprising the nucleotide substantially as set forth in <400>566.

Still yet another aspect of the present invention provides a recombinant viral construct comprising a nucleic acid molecule encoding a viral F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule comprises codons optimised for expression in a eukaryotic cell, wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein.

30 A further aspect of the present invention provides a recombinant viral construct comprising a nucleic acid molecule encoding a viral F protein variant or derivative thereof wherein

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said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein variant.

Another further aspect of the present invention relates to a vaccine comprising a
5 recombinant viral construct which construct comprises a nucleic acid molecule encoding a respiratory syncytial virus F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression in a eukaryotic cell wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein.

10

Yet another further aspect of the present invention relates to a vaccine comprising a recombinant viral construct which construct comprises a nucleic acid molecule encoding a respiratory syncytial virus F protein variant or derivative thereof, wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an
15 immune response to said F protein variant.

In accordance with these aspects of the present invention, the nucleotide sequence of the subject nucleic acid molecule is preferably the nucleotide sequence defined in <400>5, <400>6, <400>566 or <400>568.

20

Still another further aspect of the present invention provides the method of modulating at least one functional activity associated with a viral F protein in a subject, said method comprising introducing into said subject an effective amount of an F protein modulatory agent for a time and under condition sufficient for said agent to interact with said F protein.

25

Still yet another further aspect of the present invention provides a method of modulating at least one functional activity associated with a viral F protein, said method comprising contacting said viral F protein with an effective amount of an F protein modulatory agent for a time and under conditions sufficient for said agent to interact with said F protein.

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Yet still another further aspect of the present invention relates to a method for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus in a subject, said method comprising administering to said subject an effective amount of an agent, which agent is capable of down-regulating at least one functional activity of the F protein expressed by said virus, for a time and under conditions sufficient for said agent to interact with said F protein.

In still yet another aspect, the present invention relates to a method for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus in a subject, said method comprising administering to said subject an effective amount of a composition comprising an F protein or derivative thereof, F protein variant or derivative thereof and/or a nucleic acid molecule encoding said F protein or F protein variant as hereinbefore defined or a derivative, homologue, analogue, chemical equivalent a mimetic of said protein or nucleic acid molecule for a time and under conditions sufficient for said composition to down-regulate said viral F protein functional activity.

In another aspect the present invention relates to the use of an agent capable of modulating at least one functional activity of a viral F protein, which agent is identified and/or generated in accordance with the methods hereinbefore defined, in the manufacture of a medicament for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus.

In still another aspect the present invention relates to the use of a composition comprising an F protein or derivative thereof, F protein variant or derivative thereof, nucleic acid molecule encoding said F protein or F protein variant as hereinbefore defined or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein or nucleic acid molecule, in the manufacture of a medicament for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus.

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In another aspect the present invention relates to the use of an agent, which agent is identified in accordance with the methods hereinbefore defined, in the manufacture of a medicament for the modulation of at least one viral F protein associated functional activity.

- 5 Yet another aspect relates to agents for use in modulating the functional activity of a viral F protein wherein said agent is identified in accordance with the methods hereinbefore defined.

Still yet another aspect relates to agents for use in the treatment and/or prophylaxis of a
10 condition characterised by infection with a negative sense single stranded RNA virus
wherein said agent is identified in accordance with the methods hereinbefore defined.

Yet still another aspect relates to a composition comprising an F protein or derivative thereof, F protein variant or derivative thereof, a nucleic acid molecule encoding said F
15 protein or F protein variant as hereinbefore defined or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein or nucleic acid molecule for use in the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus.

20 In yet another aspect the present invention relates to a pharmaceutical composition comprising an active ingredient, as hereinbefore defined, and one or more pharmaceutically acceptable carriers and/or diluents.

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Single and three letter abbreviations used throughout the specification are defined in Table 2.

TABLE 2
5 Single and three letter amino acid abbreviations

	Amino Acid	Three-letter Abbreviation	One-letter Symbol
10	Alanine	Ala	A
	Arginine	Arg	R
	Asparagine	Asn	N
	Aspartic acid	Asp	D
	Cysteine	Cys	C
15	Glutamine	Gln	Q
	Glutamic acid	Glu	E
	Glycine	Gly	G
	Histidine	His	H
	Isoleucine	Ile	I
20	Leucine	Leu	L
	Lysine	Lys	K
	Methionine	Met	M
	Phenylalanine	Phe	F
	Proline	Pro	P
25	Serine	Ser	S
	Threonine	The	T
	Tryptophan	Trp	W
	Tyrosine	Tyr	Y
	Valine	Val	V
30	Any residue	Xaa	X

BRIEF DESCRIPTION OF THE DRAWINGS

- Figure 1a is a schematic representation of the 574 amino acid sequence of the human RSV fusion protein F. Amino acid numbers 1-22 comprises the signal sequence. The F2 subunit comprises amino acid numbers 23-130. The fusion cleavage (site 1) is amino acid numbers 131-136. Site 2 comprises residues 106-109. The F1 subunit comprises residues 136-574. The transmembrane domain is believed to span residues 525-548. The cytoplasmic domain comprises residues 549-574.
- 10 Figure 1b is a schematic representation of the amino acid sequence of the 524 residue soluble F protein. This protein is referred to as F_{sol} . F_{sol} is formed by expressing the coding sequence for F minus the residues encoding the transmembrane domain and the cytoplasmic domain of F.
- 15 Figure 1c is a schematic representation of F and F_{sol} . Cleavage positions of site 1 and site 2 are designated. Hydrophobic regions are shaded in black (from left to right, signal sequence, fusion peptide and transmembrane domain). Downward facing flags designate positions of potential N-linked glycosylation sites. The 24 amino acid region bounded by cleavage sites 1 and 2 is shown as a cross-hatched region.
- 20 Figure 2a is a schematic representation of the alignment of sequences coding for the human RSV F protein. F.viral refers to the sequence as found in wild type A2 RSV strain. F refers to the sequence which differs in 27/1725 positions from the viral sequence. Those changes were made in order to introduce unique restriction sites to the sequence. F.opt. refers to the F coding sequence which has been changed to allow for higher expression levels as outlined in the accompanying application. A total of 378/1725 nucleotides have been changed from the F.viral sequence. Underneath the boxed sequence a consensus sequence is shown.

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Figure 2b is a schematic representation of the alignment of sequences coding for the human RSV F_{sol} protein. F_{sol}.viral refers to the sequence as found in the wild type A2 RSV strain. F_{sol} refers to the sequence which differs from the viral sequence in 24/1575 nucleotides. All of these changes were incorporated to introduce unique restriction sites.

5 F_{sol}.opt. refers to the F_{sol} coding sequence optimised as described herein. A total of 334/1575 nucleotides have been changed. A consensus is shown under the boxed sequences.

Figures 3a and b are schematic representations of the DNA sequences optimised for

10 expression as cloned in the expression vector pCICO.F.FL.opt (a) and pCICO.F.opt (b). The plasmid pCICO.F.FL.opt contains the sequence referred to in Figure 2a as F.opt.. The plasmid pCICO.F.opt contains the sequence referred to in Figure 2b as F_{sol}.opt. 5' and 3' untranslated sequences not included in the Figure 2 sequences are shown in this Figure.

15 **Figures 4a and b** are schematic representations of the construction of F and F_{sol} expression vectors. These diagrams describe in detail the steps involved in constructing expression vectors pCICO.F.FL.opt and pCICO.F.opt. See text of examples for details. As previously noted pCICO.F.FL.opt contains the optimised sequence F.opt. (Figure 2a) and pCICO.F.opt contains the optimised sequence F_{sol}.opt (Figure 2b).

20 **Figure 5** is an image of an autoradiograph of a 10% SDS-PAGE gel of a immunoprecipitation of 35-S labelled supernatants from 293 cells transfected with lane (a) pCICO.FS3 (containing viral F_{sol} sequence) lane (b) pCICO.F.opt (containing optimised F_{sol} sequence). Lane (c) is from mock-transfected cells. Lane (d) contains radioactively

25 labelled molecular weight markers. The F_{sol} protein migrates at approximately 60 kd in size.

Figure 6 is a schematic representation of the alignment of sequences coding for the human RSV F protein. F.viral refers to the sequence as found in wild type A2 RS strain

30 (<400>571). F.nat refers to the sequence found in a RSV A2 cDNA clone assembled in these studies (<400>572). The two sequences differ in two places (nt 174 and 222) which

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does not effect the coding potential. Underneath the boxed sequence a consensus sequence is shown (<400>573).

Figure 7 is a western blot of protein samples derived from 293 cells transfected with WT
5 (pCICO.F.FL.opt), A2 (pCICO.F.nat) and Ctrl (control) plasmids. Cells were harvested at
24, 48 and 72 hours post transfection. Cell lysates were analysed by 12% polyacrylamide
SDS-PAGE and after electrophoresis proteins were electroblotted onto a nitrocellulose
membrane. F protein was detected as described in example 5. The immuno-reactive F
bands F1 and F1' are indicated by arrows. The position of molecular weight markers is
10 shown.

Figure 8 is photographs of 293 cells transfected with pCICO.F.FL.opt (a), pCICO.F.nat
(b) and control plasmid (c). Photographs were taken 48 hours post transfection and the
magnification is 400X. Figures a, b and c flow from top to bottom.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is predicated, in part, on the development of a negative sense single stranded RNA viral protein expression system based on optimisation of expression of the 5 viral protein encoding nucleic acid sequence such that expression of the subject nucleic acid molecule sequence by a given eukaryotic host cell is facilitated and/or improved. In a related aspect, the inventors have identified a novel cleavage site in the F viral protein, the cleavage of which is thought to be essential for the generation of a fully functionally active F protein. These developments now permit the recombinant production of viral proteins 10 and the identification and design of agents for use in modulating functional activity of the subject proteins.

Accordingly, one aspect of the present invention is directed to a method of facilitating production of a protein or derivative thereof from a negative sense single stranded RNA 15 virus, said method comprising expressing in a host cell a nucleic acid molecule encoding said protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by a eukaryotic cell.

Reference to a "negative sense single stranded RNA virus" should be understood as a 20 reference to any negative sense single stranded RNA virus, and includes, but is not limited to, viruses of the family Paramyxoviridae, Rhabdoviridae, Filoviridae, Orthomyxoviridae, Bunyaviridae or Arenaviridae. Preferably, said negative sense single stranded RNA virus is of the family Paramyxoviridae. Without limiting the present invention to any one theory 25 or mode of action, viruses of the family Paramyxoviridae are cytoplasm replicating viruses. In this regard, RNA replication involves mRNA transcription from the genomic RNA via the virion transcriptase. Utilising the protein products of this transcription, there follows the production of a full length positive stranded template which is used for the synthesis of genomic RNA. The genome is transcribed from the the 3' end by virion associated enzymes into mRNAs. Replication takes place in the cytoplasm and assembly 30 occurs via budding on the plasma membrane. The subject budding occurs through the host cell plasma membrane at sites containing the virus envelope proteins.

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Accordingly, there is more particularly provided a method of facilitating production of a protein or derivative thereof from a virus of the family Paramyxoviridae, said method comprising expressing in a host cell a nucleic acid molecule encoding said protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for
5 expression by a eukaryotic host cell.

Still more preferably, said virus is of the sub-family Pneumovirinae and most preferably said virus is respiratory syncytial virus.

- 10 Reference to a "protein from a negative sense single stranded RNA virus" should be understood as a reference to any protein which is expressed by the subject virus or a derivative of said protein. Examples of proteins include, but are not limited to, nucleocapsid associated proteins such as RNA binding proteins (e.g. N, NP), phosphoproteins (e.g. P), polymerase proteins (e.g. L), or envelope proteins (e.g. F, G, H, HN or SH). It should be understood that the subject protein may exist, in its naturally occurring form, either in isolation or fused or otherwise linked to any other proteinaceous or non-proteinaceous molecule. Preferably, the subject protein is a fusion protein, N, P or SH.
- 15
- 20 Accordingly, in one embodiment there is provided a method of facilitating production of a protein or derivative thereof from a negative sense single stranded RNA virus, which protein directly or indirectly facilitates fusion of any one or more viral components with any one or more host cell components, said method comprising expressing in a host cell a nucleic acid molecule encoding said protein or derivative thereof, the nucleotide sequence
25 of which nucleic acid molecule is optimised for expression by a eukaryotic cell.

Reference to a viral protein which "directly or indirectly facilitates fusion of any one or more viral components with any one or more host cell components" should be understood as a reference to any viral protein which functions to induce or otherwise contribute to the
30 fusion of one or more viral molecules (such as a protein or structural component) with any one or more host cell molecules. It should be understood that this activity may comprise

any one of a number of functional activities attributable to the subject protein, which other activities are not necessarily related to fusion. It should also be understood that the subject functional activity may either directly facilitate fusion or it may induce or otherwise contribute to the functioning of an unrelated molecule, which unrelated molecule directly
5 facilitates the subject fusion. Preferably the viral protein is an F protein.

This embodiment of the present invention is therefore more particularly directed to a method of facilitating production of a F protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a host cell a nucleic acid
10 molecule encoding said F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by a eukaryotic cell.

Reference to a "F protein" should be understood as a reference to the viral molecule which, *inter alia*, facilitates fusion between the virus envelope and the host cell plasma membrane
15 of infected cells. The term "F protein" should be understood to encompass all forms of F protein including, for example, any mutant, polymorphic or homologous forms of F protein. Without limiting the present invention in any way, the F protein generally comprises, at the amino terminus, an F2 portion which is linked to an F1 portion. The F1 contains a transmembrane region of the molecule which is, in turn, linked to an
20 extracellular portion of the F protein. The cytoplasmic portion of the F protein comprises the carboxy terminus. As detailed earlier, the F protein is generally synthesised in a precursor form which is activated by proteolytic cleavage at the F2/F1 junction. It is thought that this cleavage step reveals a fusion peptide which interacts with the host cell. The F2/F1 junction of the respiratory syncytial virus F protein is shown in Figure 1.

25 In another embodiment there is provided a method of facilitating production of a N protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a host cell a nucleic acid molecule encoding said N protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for
30 expression by a eukaryotic cell.

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In yet another preferred embodiment there is provided a method of facilitating production of a P protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a host cell a nucleic acid molecule encoding said P protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is
5 optimised for expression by a eukaryotic cell.

In still yet another preferred embodiment there is provided a method of facilitating production of a SH protein or derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a host cell a nucleic acid molecule
10 encoding said SH protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by a eukaryotic cell.

Preferably, the negative sense single stranded RNA virus of these preferred embodiments of the present invention is a virus of the family Paramyxoviridae. More preferably the
15 virus is of the sub-family Pneumovirinae and still more preferably the subject virus is a virus of the genus Pneumovirus. Most preferably, the virus is respiratory syncytial virus.

To the extent that it is not otherwise specified, reference to a viral "protein" extends to derivatives thereof.

20 "Derivatives" of the subject protein include fragments, parts, portions, mutants, variants and mimetics thereof including fusion proteins. Parts or fragments include, for example, active regions of the subject protein. In one aspect of the present invention, for example, the subject protein is a F protein which does not comprise the transmembrane and
25 cytoplasmic portions (herein referred to as F_{sol}). The F_{sol} fragment of the F protein is useful for X-ray crystallography and other forms of modelling for purposes such as rational drug design. Derivatives may be derived from insertion, deletion or substitution of amino acids. Amino acid insertional derivatives include amino and/or carboxylic terminal fusions as well as intrasequence insertions of single or multiple amino acids. Insertional amino
30 acid sequence variants are those in which one or more amino acid residues are introduced into a predetermined site in the protein although random insertion is also possible with

suitable screening of the resulting product. Deletional variants are characterised by the removal of one or more amino acids from the sequence. Substitutional amino acid variants are those in which at least one residue in the sequence has been removed and a different residue inserted in its place. An example of substitutional amino acid variants are

5 conservative amino acid substitutions. Conservative amino acid substitutions typically include substitutions within the following groups: glycine and alanine; valine, isoleucine and leucine; aspartic acid and glutamic acid; asparagine and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine. Additions to amino acid sequences include fusions with other peptides, polypeptides or proteins.

10

The derivatives include fragments having particular portions of the entire protein fused to peptides, polypeptides or other proteinaceous or non-proteinaceous molecules.

15 "Mutants" include variants of the subject protein which variants exhibit modified sequences, structures and/or functions. For example, the F protein variants described herein, which variants exhibit amino acid sequence alterations leading to altered cleavage properties, fall within the scope of the term "mutants".

20 The term "protein" should be understood to encompass peptides, polypeptides and proteins. The protein may be glycosylated or unglycosylated and/or may contain a range of other molecules fused, linked, bound or otherwise associated to the protein such as amino acids, lipids, carbohydrates or other peptides, polypeptides or proteins. Reference hereinafter to a "protein" includes a protein comprising a sequence of amino acids as well as a protein associated with other molecules such as amino acids, lipids, carbohydrates or 25 other peptides, polypeptides or proteins.

30 The method of the present invention is predicated on the production of a viral protein by expressing a nucleic acid molecule as herein described. In this regard, the term "expressing" should be understood to refer to the transcription and translation of a nucleic acid molecule resulting in the synthesis of a peptide, polypeptide or protein expression

product. The synthesis of an expression product via the translation step of nucleic acid molecule expression is herein referred to as "production" of that expression product.

The viral protein encoding nucleic acid molecule of the present invention is expressed in a 5 eukaryotic host cell. By "host cell" is meant any eukaryotic cell which can be transformed or transfected with a nucleotide sequence. Preferred eukaryotic host cells are mammalian cells and even more preferably 293 cells and Chinese Hamster Ovary cells.

Accordingly, there is provided a method of facilitating production of a protein or 10 derivative thereof from a negative sense single stranded RNA virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell.

15 Preferably, the subject protein is a fusion protein (more particularly the F protein), N, P or SH.

Preferably, the negative sense single stranded RNA virus of these preferred embodiments 20 of the present invention is a virus of the family Paramyxoviridae. More preferably the virus is of the sub-family Pneumovirinae and still more preferably the subject virus is a virus of the genus Pneumovirus. Most preferably, the virus is respiratory syncytial virus.

The nucleic acid molecule which is expressed in accordance with the method of the present 25 invention encodes a viral protein or derivative thereof. By "encodes" is meant that the expression product comprises the subject protein or derivative. However, it should be understood that this is not intended as a restriction in any way on the diversity of the subject expression product other than that it should comprise the subject protein or derivative thereof. For example, the nucleic acid molecule which is introduced into the host cell may encode the protein fused to another protein, peptide or polypeptide (which is 30 consistent with the definition of protein "derivative" as hereinbefore provided) or the

nucleic acid molecule may encode multiple proteins wherein at least one of those proteins is the subject protein or derivative thereof.

Reference to the subject nucleic acid molecule being "optimised" for expression by a
5 eukaryotic host cell should be understood as a reference to a nucleic acid molecule which has been mutated or otherwise varied such that its recombinant expression by a eukaryotic host cell is facilitated. Said "facilitation" includes, but is not limited to, inducing or improving levels of protein expression and/or functional activity of the expression product. Preferably, said optimisation takes the form of codon optimisation and/or nucleotide splice
10 site deletion.

By "codon optimisation" is meant that at least one codon of the naturally occurring viral protein encoding nucleotide sequence has been altered such that it encodes the same amino acid as the naturally occurring codon but uses an alternative codon to that which naturally
15 encodes the subject amino acid, which alternative codon form is more preferably expressed by a eukaryotic cell than the naturally occurring codon form.

The present invention is exemplified herein with respect to the F, P, N and SH proteins, the naturally occurring encoding nucleic acid sequences of which are defined in <400>1,
20 <400>505, <400>508 and <400>511, respectively. Without limiting the present invention to any one theory or mode of action, the inventors have determined that eukaryotic expression of a viral gene becomes possible where selected A rich and T rich regions of the naturally occurring gene are modified to express increased numbers of G rich and C rich nucleotides. This is achieved by replacing selected A or T nucleotides with a G or C
25 nucleotide, respectively. The resultant modified codon, however, preferably encodes the same amino acid as that encoded by the naturally occurring codon. With respect to the F gene, for example, the codon TTG commences at nucleotide 7 of the naturally occurring respiratory syncytial viral F protein encoding nucleic acid sequence (provided in <400>1). This codon encodes an L amino acid. In the codon optimised F protein encoding nucleic
30 acid sequence, represented herein in Figure 2a, the codon TTG is modified to read CTG, which modified codon nevertheless encodes the L amino acid. The present invention does

not, however, relate to the sequence as published by Kuhnle *et al* (1998) insofar as the sequence is used for codon optimisation.

The preferred embodiment of the present invention is to optimise the viral protein encoding nucleotide sequence such that the naturally occurring viral protein amino acid sequence or fragment thereof, is produced. However, it should be understood that it is nevertheless within the scope of the present invention to optimise a viral protein encoding nucleotide sequence in terms of expressing increased G plus C content, as required to achieve efficient mammalian host cell expression, despite the fact that an optimised codon 5 may thereafter encode an amino acid different to that originally encoded by the codon which naturally existed at that position. This may occur, for example, where the newly substituted amino acid does not significantly alter the structural and/or functional properties which are required of the recombinantly produced protein. For example, certain conservative amino acid substitutions may not alter functional properties. Similarly, amino 10 acid substitutions in regions outside the protein's functionally active regions may be acceptable in terms of the use to which the expressed protein is to be put.

15

In terms of optimising the naturally occurring F protein encoding nucleotide sequence, the number of codons which are optimised in any given situation will depend on the object to 20 be achieved. For example, optimisation of between 1 and 10 codons may be sufficient to enable production of a level of eukaryotic host cell expression sufficient for a particular purpose. However, in order to achieve still more efficient levels of expression and/or expression product functional activity, it may be desirable to optimise a larger number of codons. In this regard, in a most preferred embodiment, the optimised F, P, N and SH 25 protein encoding nucleic acid sequences correspond to the sequences defined in <400>5, <400>556, <400>559, and <400>562, respectively. However, it should be understood that the present invention extends to the use of derivatives of these sequences.

By "nucleotide splice site deletion" optimisation is meant that the nucleotide sequence 30 encoding a subject viral protein has been altered to remove one or more potential RNA splice sites. Without limiting the present invention to any one theory or mode of action, it

- is thought that inefficient expression of nucleotide sequences derived from negative sense single strand RNA viruses is due, in part, to the presence of RNA splice sites in the subject RNAs. These viruses replicate cytoplasmically in the naturally occurring host cell environment. Accordingly, there is a lack of selective pressure against RNA sequences
- 5 which comprise one or more such splice sites since the enzymes which splice eukaryotic cell RNA are generally only present in the nucleus. However, since the recombinant expression system of the present invention is based, in one embodiment, on the introduction into a eukaryotic host cell of a DNA molecule encoding the viral protein of interest, the requisite synthesis of DNA complementary to the naturally occurring viral
- 10 RNA gene would consequently also result in copying of any splice sites present in the RNA. Transcription of these DNAs will occur in the nucleus of the eukaryotic host cell thereby exposing RNA transcribed from the subject DNA to the nuclear RNA splicing enzymes of the host cell.
- 15 In terms of optimising the naturally occurring viral protein encoding nucleotide sequence, the number of splice sites which are deleted in any given situation would depend on the object to be achieved. For example, if it is desired to produce the full length viral protein, then all splice sites occurring within the protein coding region of the encoding nucleic acid molecule should be deleted. However, if it is desired to produce only a fragment of the
- 20 subject protein (for example, the F_{sol} portion of the F protein which, as hereinbefore defined, does not comprise the transmembrane and cytoplasmic regions of the F protein) then only the splice sites within that region need be removed.
- 25 Deletion of the subject splice sites is preferably achieved by substituting one or more nucleotides which comprise a splice site recognition sequence such that this sequence is no longer recognised by the relevant RNA splicing enzyme. It should be understood, however, that any other suitable method of mutating the splice site may be utilised within the context of the present invention.
- 30 The present invention is therefore preferably directed to a method of facilitating production of a protein or derivative thereof from a negative sense single stranded RNA virus, said

method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is codon optimisation and/or nucleotide splice site deletion.

5

Preferably, the subject protein is a fusion protein (more particularly the F protein), N, P or SH.

Preferably, the negative sense single stranded RNA virus is a virus of the family
10 Paramyxoviridae. More preferably the virus is of the sub-family Pneumovirinae and still more preferably the subject virus is a virus of the genus Pneumovirus. Most preferably, the virus is respiratory syncytial virus.

It should be understood that the present invention extends to the use of derivatives of the
15 optimised nucleic acid sequences.

Most preferably, said codon optimisation comprises modification of at least one A and/or T comprising codon to express G and C, respectively and said mammalian splice site deletion comprises deletion of at least one RNA splice site. To the extent that the nucleic
20 acid molecule which is introduced into the host cell is a DNA molecule, the subject deletion would relate to the region of the DNA molecule which would encode the RNA splice site.

By "derivatives" is meant nucleic acid sequences derived from single or multiple
25 nucleotide substitutions, deletions and/or additions including fusion with other nucleic acid molecules. In accordance with this definition, "derivative" therefore extends to sequences comprising any one or more of the optimised codons and/or optimised splice site regions of <400>5, <400>6, <400>556, <400>559 or <400>562.

30 Reference to a "derivative" of the subject nucleotide sequence should also be understood to extend to nucleotide sequences comprising nucleic acid substitutions, deletions or

additions other than for the purpose of optimising codons. For example, an optimised viral protein encoding nucleotide sequence may additionally comprises endonuclease restriction sites which are not expressed by the naturally occurring counterpart of the subject sequence. These may be incorporated to facilitate the generation of protein mutants. In 5 one preferred embodiment, for example, the subject nucleotide sequence derivative comprises one or more of the endonuclease restriction sites expressed in <400>3 or <400>4.

In terms of a most preferred embodiment of the present invention, <400>1 defines the 10 protein encoding region of the naturally occurring respiratory syncytial virus F protein. <400>3 defines the <400>1 sequence as modified to incorporate endonuclease restriction sites designed to facilitate the generation of protein recombinants. <400>5 defines the F protein encoding nucleotide sequence of <400>3 further modified to minimise the presence of regions which would encode RNA splice sites and to express optimised 15 codons. The amino acid sequence encoded by these nucleotide sequences is provided in <400>7.

Expression of <400>5 in accordance with the method of the present invention will be sought where production of the full length F protein is required. This may occur, for 20 example, where expression of a functional molecule is required for the performance of function based screening assays designed to detect F protein modulatory agents. However, in another embodiment, production of a portion only of the F protein may be desired. For example, production of the F_{sol} portion is particularly desirable for the purpose of 3 dimensional structural analysis, by X-ray crystallography, of the F protein active regions. 25 Furthermore, F_{sol} portion production facilitates the rational identification, modification and design of F protein modulatory agents based on analysing the agent in terms of its physical interaction with the F2 and F1 portions. In this regard, <400>2 defines the protein encoding region of the naturally occurring respiratory syncytial viral F_{sol} portion of the F protein. <400>4 defines the <400>2 sequence as modified to incorporate endonuclease 30 restriction sites designed to facilitate the generation of protein recombinants. <400>6 defines the F_{sol} protein encoding nucleotide sequence of <400>4 further modified to

minimise the presence of regions which would encode RNA splice sites and to express optimised codons. The amino acid sequence encoded by these nucleotide sequences is provided in <400>8.

- 5 According to this preferred embodiment there is provided a method of facilitating production of F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is
10 nucleotide splice site deletion.

In another preferred embodiment the present invention is directed to a method of facilitating production of a F_{sol} portion of an F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a host cell a nucleic acid
15 molecule encoding said F_{sol} portion or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is nucleotide splice site deletion.

In still another preferred embodiment there is provided a method of facilitating production
20 of F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is codon optimisation.

25 In yet another preferred embodiment the present invention is directed to a method of facilitating production of a F_{sol} portion of an F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a host cell a nucleic acid molecule encoding said F_{sol} portion or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein
30 said optimisation is codon optimisation.

In another preferred embodiment there is provided a method of facilitating production of F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is nucleotide splice site deletion and codon optimisation.

In still yet a more preferred embodiment, there is provided a method of facilitating the production of a F protein or derivative thereof from a respiratory syncytial virus, said method comprising expressing in a host cell the nucleotide sequence set forth in <400>5 or derivative thereof.

Preferably said nucleotide sequence is substantially as set forth in <400>5.

15 In another preferred embodiment, there is provided a method of facilitating the production of a F_{sol} portion of an F protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a host cell the nucleotide sequence set forth in <400>6 or derivative thereof.

20 Preferably said nucleotide sequence is substantially as set forth in <400>6.

In terms of another most preferred embodiment of the present invention, <400>555 defines the protein encoding region of the naturally occurring respiratory syncytial virus P protein. <400>556 defines the P protein encoding nucleotide sequence of <400>555 as modified to express optimised codons. The amino acid sequence encoded by this nucleotide sequences is provided in <400>554.

According to this preferred embodiment there is provided a method of facilitating production of P protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding said P protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is

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optimised for expression by said mammalian host cell wherein said optimisation is codon optimisation.

In still a more preferred embodiment, there is provided a method of facilitating the
5 production of a P protein or derivative thereof from respiratory syncytial virus, said
method comprising expressing in a host cell the nucleotide sequence set forth in <400>556
or derivative thereof.

Preferably said nucleotide sequence is substantially as set forth in <400>556.

10

In terms of yet another most preferred embodiment of the present invention, <400>558
defines the protein encoding region of the naturally occurring respiratory syncytial virus N
protein. <400>559 defines the N protein encoding nucleotide sequence of <400>558 as
modified to express optimised codons. The amino acid sequence encoded by this
15 nucleotide sequence is provided in <400>557.

According to this preferred embodiment there is provided a method of facilitating
production of N protein or derivative thereof from respiratory syncytial virus, said method
comprising expressing in a mammalian host cell a nucleic acid molecule encoding said N
20 protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is
optimised for expression by said mammalian host cell wherein said optimisation is codon
optimisation.

In still a more preferred embodiment, there is provided a method of facilitating the
25 production of a N protein or derivative thereof from respiratory syncytial virus, said
method comprising expressing in a host cell the nucleotide sequence set forth in <400>559
or derivative thereof.

Preferably said nucleotide sequence is substantially as set forth in <400>559.

30

In terms of still yet another most preferred embodiment of the present invention, <400>561 defines the protein encoding region of the naturally occurring respiratory syncytial virus SH protein. <400>562 defines the N protein encoding nucleotide sequence of <400>561 as modified to express optimised codons. The amino acid sequence encoded by this
5 nucleotide sequence is provided in <40>560.

According to this preferred embodiment there is provided a method of facilitating production of SH protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a mammalian host cell a nucleic acid molecule encoding
10 said SH protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression by said mammalian host cell wherein said optimisation is codon optimisation.

In still a more preferred embodiment, there is provided a method of facilitating the
15 production of a SH protein or derivative thereof from respiratory syncytial virus, said method comprising expressing in a host cell the nucleotide sequence set forth in <400>562 or derivative thereof.

Preferably said nucleotide sequence is substantially as set forth in <400>562.

20

In terms of performing the present invention, methods of deriving and recombinantly expressing nucleic acid molecules will be well known to those of skill in the art as will methodology directed to adding, deleting and/or substituting nucleic acids in a given nucleotide sequence.

25

In another aspect, the present invention should be understood to extend to the optimised nucleic acid molecules described herein and to the expression products derived therefrom.

30

In yet another aspect, the inventors have surprisingly determined that induction of F protein functional activity requires not one but two proteolytic cleavage events. The occurrence of these two cleavage events results in the excision of a peptide region from the

non-fully functional F protein. Prior to the advent of the present invention, it was thought that F protein activation was the result of a single cleavage event which occurred at the F2/F1 junction. Without limiting the invention to any one theory or mode of action, it is thought that the F2 portion of the non-fully functional F protein in fact comprises an 5 intervening sequence of amino acids which spans the region between the newly identified cleavage site and the F2/F1 junction and which is excised in order to facilitate formation of a functional F glycoprotein. This intervening peptide sequence is thought to comprise excess amino acids and up to three glycosylation sites depending on the particular virus strain from which the F protein is derived. Down-regulation or other form of interference 10 with cleavage at the newly identified cleavage site would therefore interfere with the induction of F protein functional activity.

Accordingly, another aspect of the present invention is directed to a method of regulating the functional activity of a viral F protein, which protein in its non-fully functional form 15 comprises an F2 portion linked, bound or otherwise associated with an F1 portion, which F2 portion comprises an intervening peptide sequence, said method comprising modulating cleavage of said intervening peptide sequence wherein excision of at least part of said intervening sequence from said non-fully functional form of said F protein up-regulates F protein functional activity.

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Reference to the subject F protein being in a "non-fully functional form" should be understood to mean that the subject F protein exhibits either no functional activity or a lesser degree of functional activity than the fully cleaved F protein, that is, the F protein which has undergone *both* cleavage events. Accordingly, "up-regulation" of F protein 25 functional activity should be understood to refer to the induction of a degree or range of functional activities greater than that exhibited by the subject F protein in its non-fully cleaved form. In its natural environment, all F proteins are synthesised in a form which comprises a F2 portion located proximally to a F1 portion. The F1 portion region of the F protein comprises a transmembrane region and an intracellular domain (Collins *et al*, 30 1996). Reference to a "non-fully functional form" of the F protein should also be understood to extend to forms of the F protein which have undergone only partial cleavage.

For example, the subject non-fully functional form of the F protein may only have undergone cleavage of the previously known cleavage site but not yet at the newly identified cleavage site.

5 Prior to the advent of the present invention, it was thought that activation of the F protein occurred following cleavage at the F protein site defined by the sequence KKRKRR (<400>563) thereby cleaving the F2 portion of the non-fully functional F protein from the F1 portion. The F1 portion of the F protein is defined, in Figure 1, as commencing at the F residue which follows the cleavage recognition site KKRKRR. However, the precise
10 location at which this cleavage event occurs is not actually known. Accordingly, it should be understood that the cleavage event may occur either between two residues located proximally to the cleavage recognition site KKRKRR or it may occur between two residues within this site. The definitions of "F2 portion", "F1 portion" and "F2/F1 junction" as provided herein should therefore be interpreted in light of this understanding.

15

As detailed above, the inventors have now determined that cleavage at this region alone will not fully activate the F protein. Rather, a second cleavage event must occur at an F protein site distinct from that of the known cleavage site (the known cleavage site being referred to as "site 1"). This second cleavage site is located in the amino terminus
20 direction of the previously known cleavage site and is characterised by expression of the cleavage recognition sequence RARR (<400>564) (herein referred to as "site 2"). When considered in light of the structure of the F protein as it was previously understood (and as depicted in Figure 1) site 2 is located within the F2 portion of the F protein while the previously known cleavage site is located at the F2/F1 portion junction.

25

For the purpose of the present invention, it should be understood that the F protein amino acid sequence located in the amino terminus direction of cleavage site 1 is herein referred to as the F2 portion while the amino acid sequence located in the carboxy terminus direction of the cleavage site 1 is herein referred to as the F1 portion. The newly identified
30 cleavage site is therefore located within the F2 portion. The F protein amino acid sequence located between the site 1 and site 2 points of cleavage is herein referred to as the

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"intervening sequence". Accordingly, in light of the definition herein provided, the "intervening sequence" forms part of the F2 portion of the non-fully functional form of the F protein. Excision of "at least part of" said intervening sequence should be understood to mean that at least a portion of the sequence which is excised following the two cleavage events is derived from the intervening sequence region as herein defined. However, it should be understood that the excised sequence may also comprise part of the non-intervening sequence region of the F2 and/or F1 portion sequences as herein defined.

Without limiting the present invention to any one theory or mode of action, it is thought that cleavage of the intervening sequence at the two cleavage sites results in complete disassociation of the intervening sequence from the F protein. Accordingly, the term "excision" is intended to encompass complete disassociation of the intervening sequence from the non-fully functional form of the F protein in order to form the functionally active F protein. However this term should also be understood to extend to a cleavage event which does not necessarily result in complete disassociation of at least part of the intervening sequence but leads to a conformational change in the secondary or tertiary structure of the intervening sequence and/or the F2/F1 portions. For example, in some circumstances an appropriate conformational shift in the intervening sequence relative to the F2 and F1 portions may be sufficient to achieve some up-regulation of the functional activity of the F protein. It should also be understood that the two cleavage events may occur concurrently in order to effect excision. Alternatively, the cleavage events may occur consecutively. For example, cleavage at site 1 may occur initially, followed by cleavage at site 2 (and hence formation of the fully functional form of the F protein) at a subsequent point in time. The present invention should also be understood to extend to a sequence of cleavage events commencing with cleavage at site 2.

The present invention is exemplified with respect to respiratory syncytial virus F protein. The respiratory syncytial virus F protein amino acid sequence is defined <400>7. In accordance with the amino acid sequence numbering provided in <400>7, the previously known cleavage site is located at the region of the F protein defined by the amino acid sequence KKRKRR, which sequence spans amino acid numbers 131 to 136 of <400>7.

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The second cleavage point, which has been identified by the present inventors, is localised to the region of the F protein defined by the amino acid sequence RARR, which sequence spans amino acid numbers 106-109 of <400>7.

- 5 In a preferred embodiment the present invention is directed to a method of regulating the functional activity of a Paramyxoviridae derived F protein, which protein in its non-fully functional form comprises an F2 portion linked, bound or otherwise associated with an F1 portion, which F2 portion comprises an intervening peptide sequence, said method comprising modulating cleavage of said intervening peptide sequence wherein excision of
10 at least part of said intervening sequence from said non-fully functional form of said F protein up-regulates F protein functional activity.

Still more preferably said F protein is derived from the Genus Pneumovirus and still more preferably said virus is respiratory syncytial virus.

- 15 In a most preferred embodiment there is provided a method of regulating the functional activity of a respiratory syncytial virus F protein, which protein in its non-fully functional form comprises an F2 portion linked, bound or otherwise associated with an F1 portion, which F2 portion comprises an intervening peptide sequence, said method comprising
20 modulating cleavage of said intervening peptide sequence, wherein excision of at least part of said intervening sequence from said non-fully functional form of said F protein up-regulates F protein functional activity and wherein said cleavage events occur at the cleavage sites defined by the peptide sequences RARR (<400>564) and KKRKRR (<400>563).

- 25 That the subject cleavage events "occur at" a given cleavage site should be understood to mean that cleavage of the F protein amino acid sequence will involve cleavage of the bonding mechanism associated with anyone or more of the amino acids comprising the defined sites. Without limiting the invention in any way, the amino acids comprising the
30 cleavage sites define the peptide sequence recognised by the proteolytic enzyme which cleaves the subject F protein (Steiner, 1998).

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In a related aspect, the present invention provides a method of regulating the functional activity of a viral F protein, which protein in its non-fully functional form comprises the structure:

5 X₁, X₂, X₃

wherein:

X₁ comprises the non-intervening peptide sequence region of the F2 portion;

X₂ comprises the intervening peptide sequence region of the F₂ portion; and

10 X₃ comprises the F1 portion

said method comprising modulating cleavage of said intervening peptide sequence wherein excision of at least part of said intervening sequence from said non-fully functional form of said F protein up-regulates F protein functional activity.

15

The representation X₁, X₂, X₃ is not to be taken as imposing any sequential constraints on the subject F protein and the present invention encompasses any conformational secondary and/or tertiary structural arrangement of X₁, X₂, X₃ to the extent that X₁ and X₃ are both linked, bound or otherwise associated with X₂ in the subject F protein's non-fully 20 functional form.

Reference to the "non-intervening peptide sequence region" of F2 should be understood as a reference to that part of the F2 subunit which does not form part of the intervening sequence as herein defined.

25

Preferably said virus is a virus from the family Paramyxoviridae and still more preferably is a virus of the Genus Pneumovirus. Most preferably said virus is respiratory syncytial virus.

In another preferred embodiment said cleavage events occur at the cleavage sites comprising X₂ and defined by the peptide sequences RARR (<400>564) and KKRKRR (<400>563).

- 5 Modulating cleavage of the intervening sequence can be achieved by any one of a number of methods including, but in no way limited to:
 - (i) Contacting the F protein or F protein encoding nucleic acid molecule with a proteinaceous or non-proteinaceous molecule (herein referred to as an "agent") which up-regulates or down-regulates cleavage of either one or both of the cleavage sites comprising the intervening sequence. The proteinaceous or non-proteinaceous molecule may achieve this objective by functioning as either an agonist or antagonist of the cleavage event, for example. This molecule may act in any one of a number of ways including interacting with the subject F protein or interacting with the enzymes which recognise the cleavage sites comprising the F protein.
 - (ii) Mutating the amino acid sequence of the F protein cleavage site such that proteolytic cleavage cannot occur. This can be performed at either the amino acid sequence level (for example by adding, substituting or deleting an amino acid in the newly identified cleavage site) or at the nucleotide level such that the transcribed and translated F protein expression product does not express a functional form of the subject cleavage site.
- 25 Said proteinaceous molecule may be derived from natural or recombinant sources including fusion proteins or following, for example, natural product screening. Said non-proteinaceous molecule may be, for example, a nucleic acid molecule or may be derived from natural sources, such as for example natural product screening or may be chemically synthesised. The present invention contemplates chemical analogues of the F protein capable of acting as agonists or antagonists of either the fully functional or non-fully functional F protein. Chemical agonists may not necessarily be derived from the F protein
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- 45 -

but may share certain conformational similarities. Alternatively, chemical agonists may be specifically designed to mimic certain physiochemical properties of the F protein. Antagonists may be any compound capable of blocking, inhibiting or otherwise preventing F protein from carrying out its normal biological function. Antagonists include 5 monoclonal antibodies specific for the F protein, or parts of the F protein, and antisense nucleic acids which prevent transcription and/or translation of the F protein encoding nucleic acid molecule or mRNA in mammalian cells.

Although the preferred method is to inhibit, retard or otherwise down-regulate F protein 10 functional activity by preventing cleavage of the non-fully functional F protein form and subsequent activation, up-regulation of F protein functional activity may be desired in certain circumstances. In this regard, use of agonistic agents which augment and/or induce the cleavage events herein described may be utilised. Reference to "down-regulating" F protein functional activity should be understood to encompass prevention of the functional 15 activation of the non-fully functional F protein.

Accordingly, in a most preferred embodiment there is provided a method of inhibiting, retarding or otherwise down-regulating the functional activity of a Paramyxoviridae derived F protein, which protein in its non-fully functional form comprises an F2 portion 20 linked, bound or otherwise associated with an F1 portion, which F2 portion comprises an intervening peptide sequence, said method comprising inhibiting or otherwise down-regulating cleavage of said intervening peptide sequence.

Preferably said F protein is derived from the Genus Pneumovirus and still more preferably 25 said virus is respiratory syncytial virus. Most preferably said cleavage events occur at the cleavage sites defined by peptide sequences RARR (<400>564) and KKRKRR (<400>563).

In another most preferred embodiment the present invention provides a method of down-regulating the functional activity of a Paramyxoviridae derived F protein, which protein in 30 its non-fully functional form comprises the structure:

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X₁X₂X₃

wherein:

- 5 X₁ comprises the non-intervening peptide sequence region of the F2 portion;
X₂ comprises the intervening peptide sequence region of the F2 portion; and
X₃ comprises the F1 portion

10 said method comprising inhibiting or otherwise down-regulating cleavage of said
intervening peptide sequence.

15 Preferably said F protein is derived from the Genus Pneumovirus and still more preferably
said virus is respiratory syncytial virus. Most preferably said cleavage events occur at the
cleavage sites defined by peptide sequences RARR (<400>564) and KKRKRR
(<400>563).

Without limiting the present invention to any one theory or mode of action, the F proteins
of viruses of the family Paramyxoviridae are involved in facilitating fusion between the
virus envelope and the host cell plasma membrane in order to effect infection. Further, it
20 is thought that the F proteins are also inserted into the host plasma membrane where,
during maturation, the virions bud through the region of the membrane containing these
proteins. Accordingly, it is thought that down-regulating F protein functional activity will
inhibit or otherwise reduce virion fusion with and infection of a potential host cell and/or
virion budding. Accordingly, the development of a method for recombinantly expressing
25 the F protein by eukaryotic cells, and in particular mammalian cells, now facilitates the
development of screening assays, utilising the F protein produced in accordance with the
method of the present invention, for the purpose of identifying agents capable of
modulating F protein functional activity, and preferably, down-regulating F protein
functional activity.

Screening for agents which modulate F protein functional activity can be achieved by any one of a number of suitable methods, which would be known to those of skill in the art, including but not limited to:

- 5 (i) High throughput screening for agents which modulate F protein functional activities utilising assays based on the detection of changes in F protein functioning. Such changes may be detected directly or indirectly.

An example of indirect detection of modulation of F protein functioning includes
10 the screening of agents on cultured cells which have been co-transfected with the F protein encoding nucleic acid molecule of the present invention and a virus which utilises the F protein in order to propagate. In this regard, either the full length F protein encoding nucleic acid sequence can be utilised or a partial sequence which encodes a functionally active F protein portion can be used. By assessing cell
15 viability it can be determined whether the subject agent inhibits or down-regulates F protein functioning thereby preventing F protein mediated propagation of cell to cell fusion. This would be evident by continued cell viability. A typical assay of this type can be performed, for example, in 293 cells which have been transiently co-transfected with a plasmid encoding the adenoviral VA RNA genes.

- 20
25 (ii) Antibody Recognition Assays

The use of antibodies which bind to conformational epitopes is a recognised method for assessing whether a protein's three dimensional structure differs from
25 the natural state. Thus an assay can be conducted on protein exposed to agents that are expected to modulate function via perturbation of the native conformation or interference with a functional conformational transition. A number of suitable F-specific antibodies and their target sites have been identified by workers in the field (see for example Lopez et al., 1998 and references therein). For example, F protein exposed to agents intended to modulate F function is subsequently incubated with F specific monoclonal antibodies using an ELISA format. Reduction or increase in F binding relative to F which has not been exposed to agents is measured by addition

of polyclonal antibody to F followed by suitable detection reagents according to standard methods.

- (iii) Immunisation leading to protection and/or virus neutralisation
- 5 RSV is known to infect a wide range of animal species when inoculated experimentally into the respiratory tract and several small animal experimental models have been described (see for example Collins et al., 1996 and references therein). These models can be used to determine whether immunisation is protective and/or results in the production of a virus neutralising response.
- 10 An example of a suitable method is as follows: Cotton rats (average weight 100 g) are anesthetized with methoxyflurane and a sample of pre-immune blood harvested via standard procedures. While anesthetized, the cotton rats are administered a suitable quantity of agent (for example, purified F protein) via an appropriate route (for example, intramuscular injection or intranasal instillation). The cotton rats are housed for an appropriate period (generally several days to weeks depending on the agents under consideration and the objectives of the study) and then anesthetized as above. Anesthetized animals are bled to obtain a post-immunization sample and infected with 100,000 plaque forming units of a suitable RSV strain (for example, RSV Long). Four days later the animals are sacrificed and lungs harvested aseptically. Protective efficacy of the agent is measured by determination of the effect on whole lung virus titre. Briefly, lungs are homogenised in sterile saline (1:10 w/v) and virus concentration determined by standard methods (for example, 15 plaque assay).
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To determine whether the agent elicited a neutralising response, pre-immunization and post-immunization samples and control samples are examined using a virus neutralization test. An example of such a test is as follows. Sera are prepared from the blood samples according to standard methods. Serial dilutions of the sera are then prepared and mixed with a known concentration of RSV (for example, 100 plaque forming units of RSV Long). Mixtures are incubated for 1 hour at room temperature before being assayed for virus concentration by standard methods (for 30

example, plaque assay). A neutralizing response is characterised by reduction in virus titre in comparison to control samples.

Accordingly, in another aspect there is provided a method for detecting an agent capable of
5 regulating the functional activity of a viral F protein or derivative thereof said method comprising contacting a eukaryotic cell expressing an optimised nucleic acid molecule encoding said viral F protein or derivative thereof, as hereinbefore described, with a putative modulatory agent and detecting an altered expression phenotype and/or functional activity.

10

It should be understood that the subject agent may act via any mechanism including, but not limited to, modulating the cleavage events hereinbefore described.

In yet another aspect there is provided a method for detecting an agent capable of
15 regulating the functional activity of a viral F protein or derivative thereof said method comprising contacting a host cell, which host cell expresses a nucleic acid molecule encoding the non-fully functional form of said viral F protein or derivative thereof as hereinbefore described, with a putative modulatory agent and detecting an altered expression phenotype and/or altered functional activity wherein said agent modulates
20 cleavage of the intervening peptide sequence.

To the extent that this aspect of the present invention is directed to screening for agents which modulate the site 2 cleavage event, it should be understood that this methodology is not limited to systems expressing an optimised nucleic acid sequence but extends to
25 systems utilising any method of expressing the subject F protein.

Reference to a "modulatory agent" should be understood as a reference to an agent which down-regulates, up regulates or otherwise alters at least one functional activity of the subject F protein. For example, the agent may increase or decrease the level of activity of
30 the F protein or it may entirely inhibit F protein functioning. Although the preferred method is to identify agents which inhibit F protein functional activity, for example by

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5 preventing cleavage of the non-fully functional form of the F protein, thereby providing a potential antiviral therapy, the identification of agents which up regulate F protein functional activity may be desired in certain circumstances. For example, it is thought that an agent which causes the F protein to prematurely initiate the conformational changes required for fusion would be inactivating.

Still more preferably, said viral F protein is a Pneumovirus F protein and yet still more preferably a respiratory syncytial virus F protein. Most preferably, said codon optimised nucleic acid molecule is the nucleic acid molecule defined in <400>5.

10

Preferably, said regulation is inhibition, retardation or other form of down-regulation.

Reference to "functional activity" should be understood as a reference to any one or more of the functions which the F protein performs. Accordingly, an agent which modulates the 15 functional activity of the F protein may modulate all or only some of the functions which the F protein performs. The phrase "functional activity" should be understood to include within its scope the cleavage events which the F protein undergoes.

In addition to screening for agents which modulate F protein functional activity utilising 20 function based assays of the type described above, the development of methodology which facilitates production of the F protein or derivatives thereof also facilitates the screening, analysis, rational design and/or modification of agents for modulating F protein functional activity based on analysis of the physical interaction of a putative agent or lead compound with the subject F protein or derivative thereof.

25

Specifically, *in vitro* production of the F protein or derivative thereof, which is now possible in light of the development of the present invention, now facilitates analysis of the tertiary structure of the F protein by techniques such as X-ray crystallography. Of particular value in this regard is the fact that the present invention permits production of 30 useful quantities of the F protein F_{sol} portion.

Accordingly, another aspect of the present invention is directed to a method for analysing, designing and/or modifying an agent capable of interacting with a viral F protein or derivative thereof and modulating at least one functional activity associated with said protein, which protein is produced in accordance with the method of the present invention
5 said method comprising contacting said F protein or derivative thereof with a putative agent and assessing the degree of interactive complementarity of said agent with said protein.

Preferably said viral F protein is a Pneumovirus F protein and even more preferably the F_{sol} portion of said Pneumovirus F protein. Still more preferably, said F_{sol} portion is defined by
10 the amino acid sequence of <400>8.

It should be understood that the F protein which is contacted with the putative agent for evaluation of interactive complementarity may be recombinantly produced. However, it should also be understood that the subject protein may take the form of an image based on
15 the structure elucidated via analysis of the F protein produced in accordance with the method of the present invention, such as an electron density map, molecular models (including, but not limited to, stick, ball and stick, space filling or surface representation models) or other digital or non-digital surface representation models or image, which facilitates the analysis of F protein: agent interactions utilising techniques and software
20 which would be known to those of skill in the art. For example, interaction analyses can be performed utilising techniques such as Biacore real-time analysis of on and off-rates and dissociation constants for binding of ligands (Gardsvoll *et al*, 1999; Hoyer-Hansen *et al*, 1997; Ploug, 1998; Ploug *et al*, 1994; 1995; 1998) and NMR perturbation studies (Stephens *et al*, 1992).

25

Reference to "assessing the degree of interactive complementarity" of an agent with the subject F protein should be understood as a reference to elucidating any feature of interest including, but not limited to, the nature and/or degree of interaction between the subject F protein and an agent of interest. As detailed above, any suitable technique can be utilised.
30 Such techniques would be known to the person of skill in the art and can be utilised in this regard. In terms of the nature of the subject interaction, it may be desirable to assess the

- types of interactive mechanisms which occur between specific residues of any given agent and those of the F protein (for example, peptide bonding or formation of hydrogen bonds, 5 ionic bonds, van der Waals forces, etc.) and/or their relative strengths. It may also be desirable to assess the degree of interaction which occurs between an agent of interest and the subject F protein. For example, by analysing the location of actual sites of interaction between the subject agent and F protein it is possible to determine the quality of fit of the agent into any region of the F protein and the relative strength and stability of that binding interaction. For example, if it is the object that F protein functioning be blocked, an agent which interacts with the F protein such that it blocks or otherwise hinders (for example, 10 sterically hinders or chemically or electrostatically repels) F2/F1 cleavage will be sought. The form of association which is required in relation to modulating F protein functioning may not involve the formation of any interactive bonding mechanism, as this is traditionally understood, but may involve a non-bonding mechanism such as the proximal location of a region of the agent relative to the subject binding region of the F protein, for 15 example, to effect steric hindrance with respect to the binding of an activating molecule. Where the interaction takes the form of hindrance or the creation of other repulsive forces, this should nevertheless be understood as a form of "interaction" despite the lack of formation of any of the traditional forms of bonding mechanisms.
- 20 It should also be understood that the F protein which is utilised either in a physical form or as an image, as hereinbefore discussed, to assess the interactive complementarity of a putative agent may be a naturally occurring form of the F protein or it may be a derivative, homologue, analogue, mutant, fragment or equivalent thereof. The derivative, homologue, analogue, mutant, fragment or equivalent thereof may take either a physical or non- 25 physical (such as an image) form.

The determination of F protein binding regions has been made possible only by development of the present invention which has permitted F protein production and thereby has facilitated determination of the three dimensional structure of the F protein and 30 the identification and/or rational modification and design of agents which can be used to modulate F protein functioning.

Without limiting the application of the present invention in any way, the method of the present invention facilitates the analysis, design and/or modification of agents capable of interacting with the F protein. In this regard, reference to "analysis, design and/or modification" of an agent should be understood in its broadest sense to include:

5

- (i) Randomly screening (for example, utilising routine high-throughput screening technology) to identify agents which exhibit some modulatory capacity with respect to F protein functional activity and then analysing the precise nature and magnitude of the agent's modulatory capacity utilising the method of this aspect of the present invention. In this regard, existing crystals could be soaked with said agents or co-crystallisation could be performed. A combination of modelling and synthetic modification of the local compound together with mutagenesis of the F protein could then be performed for example. In screening for agents which may modulate activity, standard methods of phage display and also combinatorial chemistry may be utilised (Goodson *et al.*, 1994; Terrett., 2000). Such interaction studies can also be furthered utilising techniques such as the Biacore analysis and NMR perturbation studies. Such agents are often commonly referred to as "lead" agents in terms of the random screening of proteinaceous or non-proteinaceous molecules for their capacity to function either agonistically or antagonistically.
- 10 Further, for example, binding affinity and specificity could be enhanced by modifying lead agents to maximise interactions with the F protein. Such analyses would facilitate the selection of agents which are the most suitable for a given purpose. In this way, the selection step is based not only on *in vitro* data but also on a technical analysis of sites of agent: F protein interaction in terms of their frequency, stability and suitability for a given purpose. For example, such analysis
- 15 may reveal that what appears to be an acceptable *in vitro* activity in respect of a randomly identified agent is in fact induced by a highly unstable interaction due to the presence of proximally located agent: F protein sites which exhibit significant repulsive forces thereby de-stabilising the overall interaction between the agent and the F protein. This would then facilitate the selection of another prospective lead
- 20 compound, exhibiting an equivalent degree of *in vitro* activity, but which agent
- 25
- 30

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does not, upon further analysis, involve the existence of such de-stabilising repulsive forces.

Screening for the modulatory agents herein defined can be achieved by any one of
5 several suitable methods, including in silico methods, which would be well known to those of skill in the art and which are, for example, routinely used to randomly screen proteinaceous and non-proteinaceous molecules for the purpose of identifying lead compounds.

10 These methods provide a mechanism for performing high throughput screening of putative modulatory agents such as the proteinaceous or non-proteinaceous agents comprising synthetic, recombinant, chemical and natural libraries.

15 (ii) The candidate or lead agent (for example, the agent identified in accordance with the methodology described in relation to point (i)) could be modified in order to maximise desired interactions (for example, binding affinity to specificity) with the F protein and to minimise undesirable interactions (such as repulsive or otherwise de-stabilising interactions). Such modification is only possible in light of knowledge of the three-dimensional structure of the F protein and the capacity therefore to identify regions of functional importance, thereby facilitating the structural modification of an agent to maximise an agonistic or antagonistic interaction. Such methodology is particularly applicable to rational drug design.
20

25 Methods of modification of a candidate or lead agent in accordance with the purpose as defined herein would be well known to those of skill in the art. For example, a molecular replacement program such as Amore (Navaza, 1994) may be utilised in this regard. The method of the present invention also facilitates the mutagenesis of known signal inducing agents in order to ablate or improve signalling activity.

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- (iii) In addition to analysing fit and/or structurally modifying existing molecules, the method of the present invention also facilitates the rational design and synthesis of an agent, such as an agonistic or antagonistic agent, based on theoretically modelling an agent exhibiting the desired F protein interactive structural features
5 followed by the synthesis and testing of the subject agent.

It should be understood that any one or more of applications (i) – (iii) above, may be utilised in identifying a particular agent.

- 10 In a related aspect, the present invention should be understood to extend to the agents identified utilising any of the methods hereinbefore defined. In this regard, reference to an agent should be understood as a reference to any proteinaceous or non-proteinaceous molecule which modulates at least one F protein functional activity. As hereinbefore discussed, to the extent that the present invention encompasses methods of screening for
15 agents utilising F proteins produced in accordance with the expression system hereinbefore defined, this is not to be taken as a restriction on the methodology which is employed to screen for agents which modulate the newly identified cleavage event. In this regard, the present invention extends to agents identified utilising F protein molecules or derivatives thereof howsoever produced.

20

Accordingly, the present invention is directed to an agent capable of interacting with a viral F protein and modulating at least one functional activity associated with said viral protein.

- 25 Preferably, said agent is identified in accordance with the methods hereinbefore defined.

More preferably, said agent is an antagonist which interacts with a sequence selected from:

CFASGQNITE <400>9
ASGQNITEEF <400>11
GQNITEEFYQ <400>13
NITEEFYQST <400>15
TEEFYQSTCS <400>17

FASGQNITEE <400>10
SGQNITEEFY <400>12
QNITEEFYQS <400>14
ITEEFYQSTC <400>16
EEFYQSTCSA <400>18

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EFYQSTCSAV <400>19	FYQSTCSAVS <400>20
YQSTCSAVSK <400>21	QSTCSAVSKG <400>22
STCSAVSKGY <400>23	TCSAVSKGYL <400>24
CSAVSKGYLS <400>25	SAVSKGYLSA <400>26
AVSKGYLSAL <400>27	VSKGYLSALR <400>28
SKGYLSALRT <400>29	KGYLSALRTG <400>30
GYLSALRTGW <400>31	YLSALRTGwy <400>32
LSALRTGWYT <400>33	SALRTGWYTS <400>34
ALRTGWYTTSV <400>35	LRTGWYTSVI <400>36
RTGWYTTSVIT <400>37	TGWYTTSVITI <400>38
GWYTTSVITIE <400>39	WYTTSVITIEL <400>40
YTSVITIELS <400>41	TSVITIELSN <400>42
SVTIELSNI <400>43	VITIELSNIK <400>44
ITIELSNIKK <400>45	TIELSNIKKN <400>46
IELSNIKKNK <400>47	ELSNIKKNKC <400>48
LSNIKKNKCN <400>49	SNIKKNKCNG <400>50
NIKKNKCNGT <400>51	IKKNKCNGTD <400>52
KKNKCNGTDA <400>53	KNKCNGTDAK <400>54
NKCNGTDAKV <400>55	KCNGTDAKV <400>56
CNGTDAVKVL <400>57	NGTDAVKLI <400>58
GTDAKVKLICK <400>59	TDAVKLIKQ <400>60
DAVKLIKQ <400>61	AKVKLIKQEL <400>62
KVKLIKQELD <400>63	VKLIKQELDK <400>64
KLIKQELDKY <400>65	LIKQELDKYK <400>66
IKQELDKYKN <400>67	KQELDKYKNA <400>68
QELDKYKNAV <400>69	ELDKYKNAV <400>70
LDKYKNAVTE <400>71	DKYKNAVTEL <400>72
KYKNAVTELQ <400>73	YKNAVTELQL <400>74
KNAVTELQLL <400>75	NAVTELQLLM <400>76
AVTELQLLMQ <400>77	VTELQLLMQS <400>78
TELQLLMQST <400>79	ELQLLMQSTQ <400>80
LQLLMQSTQA <400>81	QLLMQSTQAT <400>82
LLMQSTQATN <400>83	LMQSTQATNN <400>84
MQSTQATNNR <400>85	QSTQATNNRA <400>86
STQATNNRAR <400>87	TQATNNRARR <400>88
QATNNRARRE <400>89	ATNNRARREL <400>90
TNNRARREL P <400>91	NNRARRELPR <400>92
NRARRELPRF <400>93	RARRELPRFM <400>94
ARRELPRFMN <400>95	RRELPRFMNY <400>96
RELPRFMNYT <400>97	ELPRFMNYTL <400>98
LPRFMNYTLN <400>99	PRFMNYTLNN <400>100
RFMNYTLNMA <400>101	FMNYTLNNAK <400>102
MNYTLNNNAKK <400>103	NYTLNNNAKKT <400>104
YTLNNNAKKTN <400>105	TLNNNAKKTNV <400>106
LNNNAKKTNVT <400>107	NNAKKTNVTL <400>108
NAKKTNVTLS <400>109	AKKTNVTLSK <400>110
KKTNVTLSKK <400>111	KTNVTLSKKR <400>112
TNVTLSKKRK <400>113	NVTLSKKRK <400>114
VTLSKKRKRR <400>115	TLSKKRKRRF <400>116
LSKKRKRRFL <400>117	SKKRKRRLFLG <400>118
KKRKRRLFLG <400>119	KRKRRFLGFL <400>120
RKRRFLGFLL <400>121	KRRFLGFLLG <400>122
RRFLGFLGVG <400>123	RFLGFLLGVG <400>124
FLGFLLGVGSA <400>125	LGFLLGVGSA <400>126

GFLLGVGSAI	<400>127	FLLGVGSAIA	<400>128
LLGVGSIAAS	<400>129	LGVGSIAIASG	<400>130
GVGSIAASGV	<400>131	VGSIAASGVA	<400>132
GSAIASGVAV	<400>133	SAIASGVAVS	<400>134
AIASGVAVSK	<400>135	IASGVAVSKV	<400>136
ASGVAVSKVL	<400>137	SGVAVSKVLH	<400>138
GVAVSKVLHL	<400>139	VAVSKVLHLE	<400>140
AVSKVLHLEG	<400>141	VSKVLHLEGE	<400>142
SKVLHLEGEV	<400>143	KVLHLEGEVN	<400>144
VLHLEGEVNK	<400>145	LHLEGEVNKI	<400>146
HLEGEVNKIK	<400>147	LEGEVNKIKS	<400>148
EDEVNKKIKSA	<400>149	GEVNKKIKSAL	<400>150
EVNKKIKSALL	<400>151	VNKIKSALLS	<400>152
NKIKSALLST	<400>153	KIKSALLSTN	<400>154
IKSALLSTNK	<400>155	KSALLSTNKA	<400>156
SALLSTNKAV	<400>157	ALLSTNKAVV	<400>158
LLSTNKAVVS	<400>159	LSTNKAVVSL	<400>160
STNKAVVSL	<400>161	TNKAVVSLSN	<400>162
NKAVVSLNSG	<400>163	KAVVSLNSGV	<400>164
AVVSLNSNGVS	<400>165	VVSLNSNGSV	<400>166
VSLNSNGVSVL	<400>167	SLSNGVSVLT	<400>168
LSNGVSVLT	<400>169	SNGVSVLT	<400>170
NGVSVLT	<400>171	GVSVLT	<400>172
VSVLTSKVLD	<400>173	SVLTSKVLDL	<400>174
VLTSKVLDLK	<400>175	LTSKVLDLKN	<400>176
TSKVLDLKNY	<400>177	SKVLDLKNYI	<400>178
KVLDLKNYID	<400>179	VLDLKNYIDK	<400>180
LDLKNYIDKQ	<400>181	DLKNYIDKQL	<400>182
LKNYIDKQLQ	<400>183	KNYIDKQLLP	<400>184
NYIDKQLLPI	<400>185	YIDKQLLPIV	<400>186
IDKQLLPIVN	<400>187	DKQLLPIVN	<400>188
KQLLPIVNQ	<400>189	QLLPIVNQ	<400>190
LLPIVNQSC	<400>191	LPIVNQSCS	<400>192
PIVNVQSCSI	<400>193	IVNKQSCSIS	<400>194
VNKQSCSISN	<400>195	NKQSCSISNI	<400>196
KQSCSISNIE	<400>197	QSCSISNIET	<400>198
SCSISNIETV	<400>199	CSISNIETVI	<400>200
SISNIETVIE	<400>201	ISNIETVIEF	<400>202
SNIETVIEFQ	<400>203	NIETVIEFQQ	<400>204
IETVIEFQQK	<400>205	ETVIEFQQKN	<400>206
TVIEFQQKNN	<400>207	VIEFQQKNNR	<400>208
IEFQQKNNRL	<400>209	EFQQKNNRL	<400>210
FQQKNNRLLE	<400>211	QQQKNNRLLEI	<400>212
QKNNRLLEIT	<400>213	KNNRLLEITR	<400>214
NNRRLLEITRE	<400>215	NRLLEITREF	<400>216
RLLITEITREFS	<400>217	LLEITREFSV	<400>218
LEITREFSVN	<400>219	EITREFSVNA	<400>220
ITREFSVNAG	<400>221	TREFSVNAGV	<400>222
REFSVNAGVT	<400>223	EFSVNAGVTT	<400>224
FSVNAGVTT	<400>225	SVNAGVTT	<400>226
VNAGVTTPV	<400>227	NAGVTTPV	<400>228
AGVTTPVSTY	<400>229	GVTTPVSTY	<400>230
VTTPVSTYML	<400>231	TTPVSTYMLT	<400>232
TPVSTYMLTN	<400>233	PVSTYMLTN	<400>234

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VSTYMLTNSE <400>235	STYMLTNSEL <400>236
TYMLTNSELL <400>237	YMLTNSELLS <400>238
MLTNSELLSL <400>239	LTNSELLSLI <400>240
TNSELLSLIN <400>241	NSELLSLIND <400>242
SELLSLINDM <400>243	ELLSLINDMP <400>244
LLSLINDMPI <400>245	LSLINDMPIT <400>246
SLINDMPITN <400>247	LINDMPITND <400>248
INDMPITNDQ <400>249	NDMPITNDQK <400>250
DMPITNDQKK <400>251	MPITNDQKKL <400>252
PITNDQKKLM <400>253	ITNDQKKLMS <400>254
TNDQKKLMSN <400>255	NDQKKLMSNN <400>256
DQKKLMSNNV <400>257	QKKLMSNNVQ <400>258
KKLMSNNVQI <400>259	KLMSNNVQIV <400>260
LMSNNVQIVR <400>261	MSNNVQIVRQ <400>262
SNNVQIVRQQ <400>263	NNVQIVRQQS <400>264
NVQIVRQQSY <400>265	VQIVRQQSYS <400>266
QIVRQQSYSI <400>267	IVRQQSYSIM <400>268
VRQQSYSIMS <400>269	RQQSYSIMSI <400>270
QQSYSIMSII <400>271	QSYSIMSIIK <400>272
SYSIMSIIKE <400>273	YSIMSIIKEE <400>274
SIMSIIKEEV <400>275	IMSIIKEEVL <400>276
MSIIKEEVLA <400>277	SIIKEEVLAY <400>278
IIKEEVLAYV <400>279	IKEEVLAYVV <400>280
KEEVLAYVWQ <400>281	EEVLAYVWQL <400>282
EVLAYVWQLP <400>283	VLAYVWQLPL <400>284
LAYVWQLPLY <400>285	AYVWQLPLYG <400>286
YVWQLPLYGV <400>287	VVQLPLYGVI <400>288
VQLPLYGVID <400>289	QLPLYGVIDT <400>290
LPLYGVIDTP <400>291	PLYGVIDTPC <400>292
LYGVIDTPCW <400>293	YGVIDTPCWK <400>294
GVIDTPCWKL <400>295	VIDTPCWKLH <400>296
IDTPCWKLHT <400>297	DTPCWKLHTS <400>298
TPCWKLHTSP <400>299	PCWKLHTSPL <400>300
CWKLHTSPLC <400>301	WKLHTSPLCT <400>302
KLHTSPLCTT <400>303	LHTSPLCTTN <400>304
HTSPLCTTNT <400>305	TSPLCTTNTK <400>306
SPLCTTNTKE <400>307	PLCTTNTKEG <400>308
LCTTNTKEGS <400>309	CTTNTKEGSN <400>310
TTNTKEGSNI <400>311	TNTKEGSNIC <400>312
NTKEGSNICL <400>313	TKEGSNICLTI <400>314
KEGSNICLTR <400>315	EGSNICLTRT <400>316
GSNICLTRTD <400>317	SNICLTRTD <400>318
NICLTRTDRG <400>319	ICLTRTDRGW <400>320
CLTRTDRGWY <400>321	LTRTDRGWYC <400>322
TRTDRGWYCD <400>323	RTDRGWYCDN <400>324
TDRGWYCDNA <400>325	DRGWYCDNAG <400>326
RGWYCDNAGS <400>327	GWYCDNAGSV <400>328
WYCDNAGSVS <400>329	YCDNAGSVSF <400>330
CDNAGSVSFF <400>331	DNAGSVSFFP <400>332
NAGSVSFFPQ <400>333	AGSVSFFPQA <400>334
GSVSFFPQAE <400>335	SVSFFPQAET <400>336
VSFFPQAETC <400>337	SFFPQAETCK <400>338
FFPQAETCKV <400>339	FPQAETCKVQ <400>340
PQAETCKVQS <400>341	QAETCKVQSN <400>342

AETCKVQSNR	<400>343	ETCKVQSNRV	<400>344
TCKVQSNRVF	<400>345	CKVQSNRVFC	<400>346
KVQSNRVFC	<400>347	VQSNRVFCDT	<400>348
QSNRVFCDTM	<400>349	SNRVFCDTMN	<400>350
NRVFCDTMNS	<400>351	RVFCDTMNSL	<400>352
VFCDTMNSLT	<400>353	FCDTMNSLTL	<400>354
CDTMNSLTL	<400>355	DTMNSLTLPS	<400>356
TMNSLTLPS	<400>357	MNSLTLPS	<400>358
NSLTLPS	<400>359	SLTLPS	<400>360
LTLPS	<400>361	TLPSEVNLCN	<400>362
LPSEVNLCN	<400>363	PSEVNLCNVD	<400>364
SEVNLCNVDI	<400>365	EVNLNCNVDIF	<400>366
VNLCNVDIFN	<400>367	NLCNVDIFNP	<400>368
LCNVDIFNP	<400>369	CNVDIFNPKY	<400>370
NVDIFNPKYD	<400>371	VDIFNPKYDC	<400>372
DIFNPKYDCK	<400>373	IFNPKYDCKI	<400>374
FNPKYDCKIM	<400>375	NPKYDCKIMT	<400>376
PKYDCKIMTS	<400>377	KYDCKIMTSK	<400>378
YDCKIMTSKT	<400>379	DCKIMTSKTD	<400>380
CKIMTSKTDV	<400>381	KIMTSKTDVS	<400>382
IMTSKTDVSS	<400>383	MTSKTDVSSS	<400>384
TSKTDVSSSV	<400>385	SKTDVSSSVI	<400>386
KTDVSSSVIT	<400>387	TDVSSSVITS	<400>388
DVSSSVITS	<400>389	VSSSVITSLG	<400>390
SSSVITSLG	<400>391	SSVITSLGAI	<400>392
SVITSLGAI	<400>393	VITSLGAIVS	<400>394
ITSLGAI	<400>395	TSLGAI	<400>396
SLGAI	<400>397	SCY	<400>398
GAI	<400>399	GYK	<400>399
IVSCY	<400>401	GKTK	<400>400
SCYG	<400>403	KTKC	<400>402
YGK	<400>405	TAS	<400>404
KTKC	<400>407	TASNK	<400>406
KTKASNKN	<400>409	TKCTASNKR	<400>408
KTKASNKR	<400>409	CTASNKNRGI	<400>410
TASNKRGI	<400>411	ASNKRGI	<400>412
SNKRGI	<400>413	IKTF	<400>414
KNRGI	<400>415	IKTF	<400>416
RGI	<400>417	FSNG	<400>418
IKTF	<400>419	CDY	<400>420
KTF	<400>421	VSNKG	<400>422
FSNG	<400>423	CDYV	<400>424
NGCDY	<400>425	VSNKG	<400>426
CDYV	<400>427	CDYV	<400>428
YVSNKG	<400>429	VSNKG	<400>430
SNKG	<400>431	CDYV	<400>432
KGVD	<400>433	VSVGNT	<400>434
VDTV	<400>435	VGNTLY	<400>436
TVSG	<400>437	VSVGNTLYYV	<400>438
SVGNTLYYV	<400>439	VGNTLYYV	<400>440
GNTLYYV	<400>441	NTLYYV	<400>442
TLYYV	<400>443	LYYV	<400>444
YYV	<400>445	VNKG	<400>446
VNKQEGKS	<400>447	QEGKS	<400>448
VNKQEGKS	<400>447	SLYV	<400>450
KQEGKS	<400>449	VKG	<400>450

EGKSLYVKGE <400>451	GKSLYVKGEP <400>452
KSLYVKGEPI <400>453	SLYVKGEPII <400>454
LYVKGEPIIN <400>455	YVKGEPIINF <400>456
VKGEPINFY <400>457	KGEPIINFYD <400>458
GEPINFYDP <400>459	EPIINFYDPL <400>460
PIINFYDPLV <400>461	IINFYDPLVF <400>462
INFYDPLVFP <400>463	NFYDPLVFPS <400>464
FYDPLVFPSSD <400>465	YDPLVFPSSDE <400>466
DPLVFPSSDEF <400>467	PLVFPSSDEFD <400>468
LVFPSSDEFDA <400>469	VFPSSDEFDAS <400>470
FPSDEFDASI <400>471	PSDEFDASIS <400>472
SDEFDASISQ <400>473	DEFDASISQV <400>474
EFDASISQVN <400>475	FDASISQVNE <400>476
DASISQVNKEK <400>477	ASISQVNKEKI <400>478
SISQVNKEKIN <400>479	ISQVNKEKINQ <400>480
SQVNKEKINQS <400>481	QVNKEKINQL <400>482
VNEKINQSLA <400>483	NEKINQSLAF <400>484
EKINQSLAFI <400>485	KINQSLAFIR <400>486
INQSLAFIRK <400>487	NQSLAFIRKS <400>488
QSLAFIRKSD <400>489	SLAFIRKSD <400>490
LAFIRKSDDEL <400>491	AFIRKSDELL <400>492
FIRKSDELLH <400>493	IRKSDELLHN <400>494
RKSDELLHNV <400>495	KSDELLHNVN <400>496
SDELLHNVNA <400>497	DELLHNVNAG <400>498
ELLHNVNAGK <400>499	LLHNVNAGKS <400>500
LHNVNAGKST <400>501	HNVNAGKSTT <400>502
NVNAGKSTTN <400>503	VNAGKSTTNI <400>504
NAGKSTTNIM <400>505	AGKSTTNIMI <400>506
GKSTTNIMIT <400>507	KSTTNIMITT <400>508
STTNIMITTI <400>509	TTNIMITTII <400>510
TNIMITTIII <400>511	NIMITTIIIV <400>512
IMITTIIIVI <400>513	MITTIIIVII <400>514
ITIIIVIIV <400>515	TTIIIVIIVI <400>516
TIIIVIIVIL <400>517	IIIVIIVILL <400>518
IIIVIIVILS <400>519	IVIIVILLSL <400>520
VIIIVILLSLI <400>521	IIVILLSLIA <400>522
IVILLSLIAV <400>523	VILLSLIAVG <400>524
ILLSLIAVGL <400>525	LLSLIAVGLL <400>526
LSLIAVGLL <400>527	SLIAVGLLL <400>528
LIAVGLLLYC <400>529	IAVGLLLYCK <400>530
AVGLLLYCKA <400>531	VGLLLYCKAR <400>532
GLLLYCKARS <400>533	LLLYCKARST <400>534
LLYCKARSTP <400>535	LYCKARSTPV <400>536
YCKARSTPVT <400>537	CKARSTPVTL <400>538
KARSTPVTLS <400>539	ARSTPVTLSK <400>540
RSTPVTLSKD <400>541	STPVTLSKDQ <400>542
TPVTLSKDQL <400>543	PVTLSKDQLS <400>544
VTLSKDQLSG <400>545	TLSKDQLSGI <400>546
LSKDQLSGIN <400>547	SKDQLSGINN <400>548
KDQLSGINNI <400>549	DQLSGINNIA <400>550
QLSGINNIAF <400>551	LSGINNIAFS <400>552
SGINNIAFSN <400>553	

Even more preferably said antagonist interacts with a sequence selected from <400>88, <400>89, <400>90, <400>91, <400>92, <400>93 or <400>94.

- 5 Reference to "interacts" should be understood as a reference to any form of interaction including, but not limited to covalent bonds, hydrogen bonds, ionic bonds, van der Waals forces or any other interactive bonding mechanism.

Still without limiting the present invention to any one theory or mode of action the
10 inventors have determined that inhibition or other form of interference with cleavage at the newly identified cleavage site disclosed herein interferes with F protein functioning. Further, it is thought that the intervening sequence exhibits relevance in relation to immune recognition. Specifically, it is thought that F proteins engineered to either retain the intervening sequence or which are engineered such that the intervening sequence is
15 removed altogether exhibit altered but improved immunogenicity. Although not wishing to be constrained by theory, it is thought that in the normal physiological setting, the intervening sequence which is excised following formation of the fully functional F glycoprotein serves as an immune decoy thereby obstructing or otherwise inhibiting the induction of an immune response against the fully functional F protein.

20 Accordingly, mutating the cleavage sites comprising the F protein (at either the amino acid or encoding nucleic acid level) provides a useful tool for producing molecules which are engineered to retain the intervening sequence and which cannot undergo the normal cleavage event in order to generate the fully functional F protein. These molecules are
25 useful in a range of applications including, but not limited to, as an immunogen for use in a vaccination protocol. In addition to producing a F protein variant which cannot be cleaved, identification by the inventors of the second cleavage site now enables the synthesis of F protein molecules which lack the intervening sequence as herein defined. This is particularly useful since it is thought that the F protein which lacks the intervening
30 sequence, but which intervening sequence was not released into the circulation of the subject, will exhibit better immunogenicity than the naturally occurring F protein.

Accordingly, in another aspect there is provided a viral F protein variant comprising a mutation in the intervening peptide sequence wherein said variant exhibits modulated functional activity relative to wild type F protein or a derivative, homologue, analogue, chemical equivalent or mimetic of said variant.

5

More particularly, there is provided a viral F protein variant comprising a mutation in the intervening peptide sequence wherein said variant exhibits down-regulated functional activity relative to wild type F protein or a derivative, homologue, analogue, chemical equivalent or mimetic of said variant.

10

Reference to "intervening peptide sequence" should be understood to have the same meaning as hereinbefore defined.

15

Reference to "wild type" F protein is a reference to the forms of F protein which are predominantly expressed by negative sense single stranded RNA viruses. This should be understood to include reference to the uncleaved form of the F protein, the functional activity of which includes the capacity to undergo cleavage and excision of the intervening sequence, and the fully functional F protein in respect of which the intervening sequence has been excised. It should be understood that to the extent that the subject variant molecule comprises all or part of the intervening sequence, modulation of its functional activity should be assessed relative to the wild type F protein which still comprises the intervening sequence. Conversely, a variant F protein which does not comprise the intervening sequence should be assessed relative to the cleaved wild type F protein. In this regard, reference to "functional activity" should be understood as a reference to any one or more of the functional activities which the subject F protein can perform including, but not limited to, its capacity to undergo cleavage or its capacity to induce an immune response.

25

Reference to "mutation" should be understood as a reference to any change, alteration or other modification, whether occurring naturally or non-naturally, which results in the subject F protein exhibiting functional activity which is modulated relative to that of the corresponding wild type F protein.

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- The change, alteration or other modification may take any form including, but not limited to, a structural modification (such as an alteration secondary, tertiary or quaternary structure of the F protein molecule), a molecular modification (such as an addition substitutational deletion of one or more amino acids from the F protein) or a chemical
- 5 modification. The subject modification should also be understood to extend to the fusion, linking or binding of a proteinaceous or non-proteinaceous molecule to the F protein or to the nucleic acid molecule encoding the F protein thereby rendering the expression product functionally distinctive over the corresponding wild type F protein. It should also be understood that although it is necessary that the subject mutation is expressed by the F
- 10 protein expression product, the creation of the mutation may be achieved by any suitable means including either mutating a wild type F protein, synthesising a F protein variant or modifying a nucleic acid molecule encoding a wild type F protein such that the expression product of said mutated nucleic acid molecule is a F protein variant. Preferably, said mutation is a single or multiple amino acid sequence substitution, addition and/or deletion.
- 15 In this regard, in one preferred embodiment the subject mutation is deletion of all or part of the intervening sequence. In another preferred embodiment, the subject mutation is an amino acid substitution which renders the newly identified cleavage site inactive. By inactive is meant that the cleavage site cannot be cleaved by the enzymatic processes which normally function to activate an F protein *in vivo*.
- 20 In a preferred embodiment the viral F protein is a Paramyxoviridae F protein and still more preferably the subject viral F protein is of the Genus Pneumovirus and still more preferably respiratory syncytial virus.
- 25 In a most preferred embodiment there is provided a respiratory syncytial virus F protein variant comprising a mutation in the cleavage site defined by amino acids RARR (<400>564) wherein said variant exhibits down-regulated functional activity relative to wild type F protein or a derivative, homologue, analogue, chemical equivalent or mimetic of said variant.

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Preferably said mutation comprises one or more of the amino acid substitutions selected from the following list:

- (i) R106G
- 5 (ii) A107Q
- (iii) R108G

Still more preferably said F protein variant comprises the sequence substantially as set forth in <400>565.

10

In another preferred embodiment there is provided a respiratory syncytial virus F protein variant comprising a multiple amino acid deletion from the intervening peptide sequence wherein said variant exhibits down-regulated functional activity relative to wild type F protein or a derivative, homologue, analogue, chemical equivalent of said variant.

15

It is more preferably provided that said amino acid deletion is a partial deletion of the intervening peptide sequence and more preferably a deletion of the peptide sequence

RARRELPRFMNYTLNNAKKTNVTLS <400>569.

20

Still more preferably said variant comprises the amino acid sequence substantially as set forth in <400>567.

To the extent that the present invention relates to F protein variants comprising one or 25 more amino acid additions, substitutions and/or deletions, it should also be understood to extend to nucleic acid molecules encoding said variants.

Accordingly, another aspect of the present invention is directed to an isolated nucleic acid molecule selected from the list consisting of:

- 30 (i) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F

protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a mutation in the intervening peptide sequence wherein said variant exhibits modulated functional activity relative to wild-type F protein.

5

(ii) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a mutation in the intervening peptide sequence wherein said variant exhibits down-regulated functional activity relative to wild-type F protein.

10

(iii) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a respiratory syncytial virus F protein or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a mutation in the cleavage site defined by amino acids RARR wherein said variant exhibits down-regulated functional activity relative to wild-type F protein.

15

(iv) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a respiratory syncytial virus F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises one or more of the amino acid substitutions selected from the following list:

20

- (a) R106G
- (b) A107Q
- (c) R108G

(v) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F

25

protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a multiple amino acid deletion from the intervening peptide sequence wherein said variant exhibits down-regulated functional activity relative to wild-type F protein.

5

- (vi) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a partial deletion of the intervening peptide sequence and more preferably a deletion of the peptide sequence

10

RARRELPRFMNYTLNNAKKTNVTLS <400>569.

15

- (vii) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises the amino acid sequence substantially as set forth in <400>567.

20

- (viii) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises the amino acid sequence substantially as set forth in <400>565.

25

- (ix) An isolated nucleic acid molecule or derivative or analogue thereof comprising the nucleotide substantially as set forth in <400>568.
- (x) An isolated nucleic acid molecule or derivative or analogue thereof comprising the nucleotide substantially as set forth in <400>566.

30

In a preferred embodiment the viral F protein is a Paramyxoviridae F protein and still more preferably the subject viral F protein is of the Genus Pneumovirus and still more preferably respiratory syncytial virus.

- 5 The nucleic acid molecule of the subject invention may be ligated to an expression vector capable of expression in a prokaryotic cell (eg. *E.Coli*) or a eukaryotic cell (eg. yeast cells, fungal cells, insect cells, mammalian cells or plant cells). The nucleic acid molecule may be ligated or fused or otherwise associated with a nucleic acid molecule encoding another entity such as, for example, a signal peptide. It may also comprise additional nucleotide sequence information fused, linked or otherwise associated with it either at the 3' or 5'
10 terminal portions or at both the 3' and 5' terminal portions. The nucleic acid molecule may also be part of a vector, such as an expression vector. The latter embodiment facilitates production of recombinant forms of the variant F protein encompassed by the present invention.
- 15 The variant F protein molecule of the present invention may be derived from natural or recombinant sources or may be chemically synthesised. Methods for producing these molecules would be well known to those skilled in the art.
- 20 As hereinbefore provided, "derivatives" include fragments, parts, portions, variants and mimetics from natural, synthetic or recombinant sources including fusion proteins. Parts or fragments include, for example, active regions of F protein. Derivatives may be derived from insertion, deletion or substitution of amino acids. Amino acid insertional derivatives include amino and/or carboxylic terminal fusions as well as intrasequence insertions of
25 single or multiple amino acids. Insertional amino acid sequence variants are those in which one or more amino acid residues are introduced into a predetermined site in the protein although random insertion is also possible with suitable screening of the resulting product. Deletional variants are characterised by the removal of one or more amino acids from the sequence. Substitutional amino acid variants are those in which at least one residue in the sequence has been removed and a different residue inserted in its place. An example of substitutional amino acid variants are conservative amino acid substitutions.
30

Conservative amino acid substitutions typically include substitutions within the following groups: glycine and alanine; valine, isoleucine and leucine; aspartic acid and glutamic acid; asparagine and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine. Additions to amino acid sequences include fusions with other peptides,
5 polypeptides or proteins.

Reference to "homologues" should be understood as a reference to F protein nucleic acid molecules or proteins derived from viral strains other than the species of origin.

- 10 Chemical and functional equivalents of F protein nucleic acid or protein molecules should be understood as molecules exhibiting any one or more of the functional activities of these molecules and may be derived from any source such as being chemically synthesized or identified via screening processes such as natural product screening.
- 15 The derivatives include fragments having particular epitopes or parts of the entire protein fused to peptides, polypeptides or other proteinaceous or non-proteinaceous molecules.

Analogues contemplated herein include, but are not limited to, modification to side chains, incorporating of unnatural amino acids and/or their derivatives during peptide, polypeptide
20 or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecules or their analogues.

Derivatives of nucleic acid sequences may similarly be derived from single or multiple nucleotide substitutions, deletions and/or additions including fusion with other nucleic acid
25 molecules. The derivatives of the nucleic acid molecules of the present invention include oligonucleotides, PCR primers, antisense molecules, molecules suitable for use in cosuppression and fusion of nucleic acid molecules. Derivatives of nucleic acid sequences also include degenerate variants.

- 30 Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with NaBH₄; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate;

trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with NaBH₄.

- 5 The guanidine group of arginine residues may be modified by the formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

- The carboxyl group may be modified by carbodiimide activation *via* O-acylisourea
10 formation followed by subsequent derivitisation, for example, to a corresponding amide.

- Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride
15 or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH.

- 20 Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.
25 Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carboethoxylation with diethylpyrocarbonate.

- Examples of incorporating unnatural amino acids and derivatives during protein synthesis
30 include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl

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alanine and/or D-isomers of amino acids. A list of unnatural amino acids contemplated herein is shown in Table 3.

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TABLE 3

	Non-conventional amino acid	Code	Non-conventional amino acid	Code
5	α -aminobutyric acid	Abu	L-N-methylalanine	Nmala
	α -amino- α -methylbutyrate	Mgabu	L-N-methylarginine	Nmarg
	aminocyclopropane- carboxylate	Cpro	L-N-methyleasparagine	Nmasn
10	aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
	aminonorbornyl- carboxylate	Norb	L-N-methylglutamine	Nmgln
	cyclohexylalanine	Chexa	L-N-methylglutamic acid	Nmglu
	cyclopentylalanine	Cpen	L-N-methylisoleucine	Nmile
15	D-alanine	Dal	L-N-methylleucine	Nmleu
	D-arginine	Darg	L-N-methyllysine	Nmlys
	D-aspartic acid	Dasp	L-N-methylmethionine	Nmmet
	D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
	D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
20	D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
	D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
	D-isoleucine	Dile	L-N-methylproline	Nmpro
	D-leucine	Dleu	L-N-methylserine	Nmser
	D-lysine	Dlys	L-N-methylthreonine	Nmthr
25	D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
	D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
	D-phenylalanine	Dphe	L-N-methylvaline	Nmval
	D-proline	Dpro	L-N-methylethylglycine	Nmetg
	D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
30	D-threonine	Dthr	L-norleucine	Nle
	D-tryptophan	Dtrp	L-norvaline	Nva
	D-tyrosine	Dtyr	α -methyl-aminoisobutyrate	Maib
	D-valine	Dval	α -methyl- -aminobutyrate	Mgabu

	D- α -methylalanine	Dmala	α -methylcyclohexylalanine	Mchexa
	D- α -methylarginine	Dmarg	α -methylcyclopentylalanine	Mcpen
	D- α -methylasparagine	Dmasn	α -methyl- α -naphthylalanine	Manap
	D- α -methylaspartate	Dmasp	α -methylpenicillamine	Mpen
5	D- α -methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
	D- α -methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
	D- α -methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
	D- α -methylisoleucine	Dmile	N-amino- α -methylbutyrate	Nmaabu
	D- α -methylleucine	Dmleu	α -naphthylalanine	Anap
10	D- α -methyllysine	Dmlys	N-benzylglycine	Nphe
	D- α -methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Ngln
	D- α -methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
	D- α -methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
	D- α -methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
15	D- α -methylserine	Dmser	N-cyclobutylglycine	Ncbut
	D- α -methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
	D- α -methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
	D- α -methyltyrosine	Dmty	N-cyclodecylglycine	Ncdec
	D- α -methylvaline	Dmval	N-cyclododecylglycine	Ncdod
20	D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
	D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
	D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
	D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
	D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
25	D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
	D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr
	D-N-methylhistidine	Dnmhis	N-(hydroxyethyl)glycine	Nser
	D-N-methylisoleucine	Dnmile	N-(imidazolylethyl)glycine	Nhis
	D-N-methylleucine	Dnmleu	N-(3-indolyethyl)glycine	Nhtrp
30	D-N-methyllysine	Dnmlys	N-methyl- γ -aminobutyrate	Nmgabu
	N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmet
	D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	Nmcpen
	N-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe

	N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
	N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
	N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
	D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
5	D-N-methyltyrosine	Dnmtyr	N-methyla-naphthylalanine	Nmanap
	D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
	γ -aminobutyric acid	Gabu	N-(<i>p</i> -hydroxyphenyl)glycine	Nhtyr
	L- <i>t</i> -butylglycine	Tbug	N-(thiomethyl)glycine	Ncys
	L-ethylglycine	Etg	penicillamine	Pen
10	L-homophenylalanine	Hphe	L- α -methylalanine	Mala
	L- α -methylarginine	Marg	L- α -methylasparagine	Masn
	L- α -methylaspartate	Masp	L- α -methyl- <i>t</i> -butylglycine	Mtbug
	L- α -methylcysteine	Mcys	L-methylethylglycine	Metg
	L- α -methylglutamine	Mgln	L- α -methylglutamate	Mglu
15	L- α -methylhistidine	Mhis	L- α -methylhomophenylalanine	Mhphe
	L- α -methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
	L- α -methylleucine	Mleu	L- α -methyllysine	Mlys
	L- α -methylmethionine	Mmet	L- α -methylnorleucine	Mnle
	L- α -methylnorvaline	Mnva	L- α -methylornithine	Morn
20	L- α -methylphenylalanine	Mphe	L- α -methylproline	Mpro
	L- α -methylserine	Mser	L- α -methylthreonine	Mthr
	L- α -methyltryptophan	Mtrp	L- α -methyltyrosine	Mtyr
	L- α -methylvaline	Mval	L-N-methylhomophenylalanine	Nmhphe
	N-(N-(2,2-diphenylethyl)	Nnbhm	N-(N-(3,3-diphenylpropyl)	Nnbhe
25	carbamylmethyl)glycine		carbamylmethyl)glycine	
	1-carboxy-1-(2,2-diphenyl-Nmbo ethylamino)cyclopropane			

-
- 30 Crosslinkers can be used, for example, to stabilise 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with n=1 to n=6, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional

reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety.

In addition to screening for agents which modulate F protein functional activity, the 5 development of a method of producing a viral F protein or derivative thereof in a eukaryotic cell and identification of the novel F protein cleavage site has now facilitated the development of *in vivo* methodology directed to administering to a subject a vaccine comprising a nucleic acid molecule encoding a viral F protein or derivative thereof. Reference to "derivative" should be understood to encompass variants thereof, such as the 10 variants hereinbefore defined. Without limiting the present invention to any one theory or mode of action, the operation of such a vaccine is based on the generation of an immune response, in particular antibody synthesis, directed to the subject F protein or derivative thereof. The antibodies generated therein bind to virally produced F proteins thereby inhibiting their fusion related functional activity and consequently reducing and/or 15 inhibiting further viral propagation. Such a vaccine is useful in either the prophylactic and/or therapeutic sense.

Accordingly, another aspect of the present invention provides a recombinant viral construct comprising a nucleic acid molecule encoding a viral F protein or derivative 20 thereof, the nucleotide sequence of which nucleic acid molecule comprises codons optimised for expression in a eukaryotic cell, wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein.

25 Still another aspect of the present invention provides a recombinant viral construct comprising a nucleic acid molecule encoding a viral F protein variant or derivative thereof wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein variant.

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In a preferred embodiment the viral F protein is a Paramyxoviridae F protein and still more preferably the subject viral F protein is of the Genus Pneumovirus and still more preferably respiratory syncytial virus.

- 5 Reference to "inducing, enhancing or otherwise stimulating" an immune response to an F protein should be understood to mean stimulating or facilitating the stimulation of a specific immune response. The specific immune response is preferably a humoral response which is directed to any one or more regions of the F protein. In this regard, it should be understood that the subject immune response will down-regulate and/or inhibit
- 10 at least one functional activity of the subject F protein.

Yet another aspect of the present invention relates to a vaccine comprising a recombinant viral construct which construct comprises a nucleic acid molecule encoding a respiratory syncytial virus F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule is optimised for expression in a eukaryotic cell wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein.

Still another aspect of the present invention relates to a vaccine comprising a recombinant viral construct which construct comprises a nucleic acid molecule encoding a respiratory syncytial virus F protein variant or derivative thereof, wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein variant.

- 25 In accordance with these aspects of the present invention, the nucleotide sequence of the subject nucleic acid molecule is preferably the nucleotide sequence defined in <400>5, <400>6, <400>566 or <400>568.

A further aspect of the present invention relates to use of the agents hereinbefore defined to modulate F protein functional activity and, in particular, the use of these agents in the therapeutic and/or prophylactic treatment of conditions characterised by infection with a

negative sense single stranded RNA virus, and more particularly respiratory syncytial virus. Conditions envisaged herein include Parainfluenza induced croup and bronchiolitis. It should be understood that reference to "agent" hereinafter includes reference to agents identified or generated by the screening assays described above, including the modulatory

5 agents (for example, antibodies) which are generated *in vivo* via use of a DNA vaccine. This aspect of the present invention is also directed to use of the F protein or derivatives thereof or encoding nucleic acid molecules, including the F protein variants, as hereinbefore described in the therapeutic and/or prophylactic treatment of conditions characterised by infection with a negative sense single stranded RNA virus.

10

Accordingly, another aspect of the present invention provides the method of modulating at least one functional activity associated with a viral F protein in a subject, said method comprising introducing into said subject and effective amount of an F protein modulatory agent for a time and under condition sufficient for said agent to interact with said F protein.

15

Preferably, said functional activity is F protein mediated host cell-virion fusion and/or virion budding and said modulation is down-regulation.

In a preferred embodiment the viral F protein is a Paramyxoviridae F protein and still more 20 preferably the subject viral F protein is of the Genus Pneumovirus and still more preferably respiratory syncytial virus.

The term "subject" includes humans primates, livestock animals(eg, horses, cattle, sheep, pigs, donkeys), laboratory test animals (eg, mice, rats, rabbits, guinea pigs), companion 25 animals (eg, dogs, cats), captive wild animals (eg, kangaroos, deer, foxes), birds (eg, chickens, ducks, bantams, pheasants). Preferably the subject is a human or laboratory test animal. Even more preferably the subject is a human.

In another aspect, the present invention provides a method of modulating at least one 30 functional activity associated with a viral F protein, said method comprising contacting

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said viral F protein with an effective amount of an F protein modulatory agent for a time and under conditions sufficient for said agent to interact with said F protein.

Preferably said viral F protein is a Pneumovirus F protein and even more preferably a respiratory syncytial virus F protein. Still more preferably said modulation is down-regulation of F protein functional activity.

This aspect of the present invention should be understood to extend to the modulation of F protein associated functional activities in *in vitro* culture systems. This may be of benefit, 10 for example, when applied to *in vitro* procedures designed to virally infect a prospective host cell. This may be of particular use, for example, where it is desired to create a cell line or to otherwise create a virally transformed cell. In this regard, the subject modulation would preferably be up-regulation of F protein functional activity.

15 In yet another aspect, the present invention relates to a method for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus in a subject, said method comprising administering to said subject an effective amount of an agent, which agent is capable of down-regulating at least one functional activity of the F protein expressed by said virus, for a time and under conditions sufficient 20 for said agent to interact with said F protein.

In still yet another aspect, the present invention relates to a method for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus in a subject, said method comprising administering to said subject an effective 25 amount of a composition comprising an F protein or derivative thereof, F protein variant or derivative thereof and/or a nucleic acid molecule encoding said F protein or F protein variant as hereinbefore defined or a derivative, homologue, analogue, chemical equivalent a mimetic of said protein or nucleic acid molecule for a time and under conditions sufficient for said composition to down-regulate said viral F protein functional activity.

In a preferred embodiment the viral F protein is a Paramyxoviridae F protein and still more preferably the subject viral F protein is of the Genus Pneumovirus and still more preferably respiratory syncytial virus.

- 5 Reference to "administering" an agent should be understood to extend to the administration of a DNA vaccine for the purpose of *in vivo* generation of anti – F protein antibodies.

- Reference to a condition "characterised by infection with a negative sense single stranded RNA virus" should be understood as a reference to a condition, one or more symptoms of
10 which are directly or indirectly induced due to infection of the subject with the subject virus. Preferably, said virus is a Pneumovirus and even more preferably respiratory syncytial virus.

- 15 The molecule which may be administered to a subject in accordance with the present invention may also be linked to a targeting means such as a monoclonal antibody, which provides specific delivery of the molecule to the target cells.

In a preferred embodiment the subject of the prophylactic or therapeutic treatment is a mammal and still more preferably a human.

- 20 Administration of the subject modulatory agent or the subject F protein or derivative thereof, F protein variant or derivative thereof, nucleic acid molecule encoding said F protein or F protein variant as hereinbefore defined or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein or nucleic acid molecule (hereinafter said 25 modulatory agents, proteins and/or nucleic acid molecules are collectively referred to as the "active ingredients"), in the form of a pharmaceutical composition, may be performed by any convenient means. The active ingredients of the pharmaceutical composition are contemplated to exhibit therapeutic activity when administered in an amount which depends on the particular case. The variation depends, for example, on the human or 30 animal and the active ingredient chosen. A broad range of doses may be applicable. Considering a patient, for example, from about 0.1 mg to about 1 mg of active ingredient

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may be administered per kilogram of body weight per day. Dosage regimes may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily, weekly, monthly or other suitable time intervals or the dose may be proportionally reduced as indicated by the exigencies of the situation. The active
5 ingredient may be administered in the form of pharmaceutically acceptable nontoxic salts, such as acid addition salts or metal complexes, e.g. with zinc, iron or the like (which are considered as salts for purposes of this application). Illustrative of such acid addition salts are hydrochloride, hydrobromide, sulphate, phosphate, maleate, acetate, citrate, benzoate, succinate, malate, ascorbate, tartrate and the like. If the active ingredient is to be
10 administered in tablet form, the tablet may contain a binder such as tragacanth, corn starch or gelatin; a disintegrating agent, such as alginic acid; and a lubricant, such as magnesium stearate.

Routes of administration include, but are not limited to, respiratorily, intratracheally,
15 nasopharyngeally, intravenously, intraperitoneally, subcutaneously, intracranially, intradermally, intramuscularly, intraocularly, intrathecally, intracerebrally, intranasally, infusion, orally, rectally, *via* IV drip patch and implant. Preferably, the route of administration is a route which permits directed delivery of the modulatory agent. For example, aerosol administration (such as by nebulisation) into the airways permits directed
20 delivery to the airways region, in contrast to systemic delivery which results in delivery to the whole body.

Where the disorder which is the subject of treatment or prophylaxis is a respiratory distress syndrome, delivery of the active ingredient to the airway, for example as an aerosol *via* nebulisation, is an ideal approach since this maximises delivery to the airway where the infection has occurred and minimises systemic delivery which may be associated with side effects.
25

The term "aerosol" is used in its most general sense to include any formulation capable of
30 administration *via* nasal, pharyngeal, tracheal, bronchial or oral passages. Aerosols generally comprise particles of liquid or solid suspended in a gas or vapour. Conveniently,

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the aerosol is a colloidal system such as a mist in which the dispersion medium is a gas. The method of administering the aerosol formulation is not critical and may be achieved using a nasal spray hand pump, electric pump, pressurised dispenser, nasal drip or other convenient means. Alternatively, the formulation may be administered in a dry powder delivery system. It should be understood that the method of the present invention extends to direct application of said formulations to intra nasal surfaces. In a particularly preferred embodiment, the aerosol is delivered at a rate of from about 1 to about 20 litres/min. and preferably from about 2 to about 15 litres/min. at a droplet size of from about 0.1 to about 10 μm and more preferably from about 0.1 to about 6 μm . Conveniently, a stock solution of material is prepared at a concentration of from about 0.5 to about 20 mg/ml or more preferably from about 1.0 to about 10 mg/ml of carrier solution.

The formulation is administered in a therapeutically effective amount. A therapeutically effective amount means that amount necessary at least partly to attain the desired effect, or to delay the onset of, inhibit the progression of, or halt altogether, the onset or progression of the particular condition being treated. Such amounts will depend, of course, on the particular conditions being treated, the severity of the condition and individual patient parameters including age, physical conditions, size, weight and concurrent treatment. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgement. It will be understood by those of ordinary skill in the art, however, that a lower dose or tolerable dose may be administered for medical reasons, psychological reasons or for virtually any other reasons.

Generally, daily doses of formulation will be from about 0.01 $\mu\text{g}/\text{kg}$ per day to 1000 mg/kg per day. Small doses (0.01-1 mg) may be administered initially, followed by increasing doses up to about 1000 mg/kg per day. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localised delivery route) may be employed to the extent patient tolerance permits. A single dose may be administered or multiple doses may be required on an hourly, daily, weekly or

monthly basis. Effective amounts of formulation vary depending on the individual but may range from about 0.1 µg to about 20 mg, alternatively from about 1 µg to about 10 mg and more preferably from about 1 µg to 5 mg per dose.

- 5 In another aspect the present invention relates to the use of an agent capable of modulating at least one functional activity of a viral F protein, which agent is identified and/or generated in accordance with the methods hereinbefore defined, in the manufacture of a medicament for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus.

10

- In still another aspect the present invention relates to the use of a composition comprising an F protein or derivative thereof, F protein variant or derivative thereof, nucleic acid molecule encoding said F protein or F protein variant as hereinbefore defined or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein or nucleic acid molecule, in the manufacture of a medicament for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus.

15
20 In a preferred embodiment the viral F protein is a Paramyxoviridae F protein and still more preferably the subject viral F protein is of the Genus Pneumovirus and still more preferably respiratory syncytial virus.

25 In another aspect the present invention relates to the use of an agent, which agent is identified in accordance with the methods hereinbefore defined, in the manufacture of a medicament for the modulation of at least one viral F protein associated functional activity.

25

In a preferred embodiment the viral F protein is a Paramyxoviridae F protein and still more preferably the subject viral F protein is of the Genus Pneumovirus and still more preferably respiratory syncytial virus.

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Yet another aspect relates to agents for use in modulating the functional activity of a viral F protein wherein said agent is identified in accordance with the methods hereinbefore defined.

- 5 Still yet another aspect relates to agents for use in the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus wherein said agent is identified in accordance with the methods hereinbefore defined.

- 10 Yet still another aspect relates to a composition comprising an F protein or derivative thereof, F protein variant or derivative thereof, a nucleic acid molecule encoding said F protein or F protein variant as hereinbefore defined or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein or nucleic acid molecule for use in the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus.

15

In a preferred embodiment the viral F protein is a Paramyxoviridae F protein and still more preferably the subject viral F protein is of the Genus Pneumovirus and still more preferably respiratory syncytial virus.

- 20 Reference herein to "treatment" and "prophylaxis" is to be considered in its broadest context. The term "treatment" does not necessarily imply that a mammal is treated until total recovery. Similarly, "prophylaxis" does not necessarily mean that the subject will not eventually contract a disease condition. Accordingly, treatment and prophylaxis include amelioration of the symptoms of a particular condition or preventing or otherwise reducing
25 the risk of developing a particular condition. The term "prophylaxis" may be considered as reducing the severity of onset of a particular condition. "Treatment" may also reduce the severity of an existing condition or the frequency of acute attacks.

- 30 In accordance with these methods, the active ingredients defined in accordance with the present invention may be coadministered with one or more other compounds or molecules. By "coadministered" is meant simultaneous administration in the same formulation or in

two different formulations via the same or different routes or sequential administration by the same or different routes. By "sequential" administration is meant a time difference of from seconds, minutes, hours or days between the administration of the two types of molecules. These molecules may be administered in any order.

5

In yet another aspect the present invention relates to a pharmaceutical composition comprising an active ingredient, as hereinbefore defined, and one or more pharmaceutically acceptable carriers and/or diluents.

- 10 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion or may be in the form of a cream or other form suitable for topical application. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of
- 15 microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion
- 20 and by the use of surfactants. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the
- 25 compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

- Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients
- 30 enumerated above, as required, followed by filtered sterilisation. Generally, dispersions are prepared by incorporating the various sterilised active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those

enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

5

When the active ingredients are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the

10 active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The

15 amount of active compound in such therapeutically useful compositions in such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.1

μg and 2000 mg of active compound.

20 The tablets, troches, pills, capsules and the like may also contain the components as listed hereafter: a binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose,

lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or

25 elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically

30

pure and substantially non-toxic in the amounts employed. In addition, the active compound(s) may be incorporated into sustained-release preparations and formulations.

Pharmaceutical compositions suitable for aerosol administration have been hereinbefore
5 described.

The pharmaceutical composition may also comprise genetic molecules such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule encoding an active ingredient. The vector may, for example, be a viral vector.

10

The present invention is further described by the following non-limiting examples.

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TABLE 1

Sequence ID Number	Description
<400>1	Natural F protein nucleic acid sequence
<400>2	Natural F _{sol} portion nucleic acid sequence
5 <400>3	Restriction site modified F protein nucleic acid sequence
<400>4	Restriction site modified F _{sol} portion nucleic acid sequence
<400>5	Splice site and codon optimised F protein nucleic acid sequence
10 <400>6	Splice site and codon optimised F _{sol} portion nucleic acid sequence
<400>7	F protein amino acid sequence
<400>8	F _{sol} portion amino acid sequence
<400>9 - <400>553	F protein amino acid decapeptides
<400>554	P protein amino acid sequence
15 <400>555	Natural P protein nucleic acid sequence
<400>556	Optimised P protein nucleic acid sequence
<400>557	N protein amino acid sequence
<400>558	Natural N protein nucleic acid sequence
<400>559	Optimised N protein nucleic acid sequence
20 <400>560	SH protein amino acid sequence
<400>561	Natural SH protein nucleic acid sequence
<400>562	Optimised SH protein nucleic acid sequence
<400>563	F protein cleavage site 1 aa sequence
<400>564	F protein cleavage site 2 aa sequence
25 <400>565	F protein variant
<400>566	F protein variant nucleic acid sequence
<400>567	F protein variant
<400>568	F protein variant nucleic acid sequence
<400>569	F protein intervening aa sequence
30 <400>570	Poly (a) adenylation site

EXAMPLE 1
DESIGN OF SYNTHETIC GENE FOR RSV F EXPRESSION

Initial attempts to express the RSV F gene sequence in a soluble form (truncated at the transmembrane domain) proved unsuccessful in achieving high levels of expression. The sequence used in the expression vectors was called F._{sol}. (this differed from the viral sequence in 24/1575 nucleotides where restriction sites had been inserted to allow for easy mutagenesis – see Fig. 2b). The F viral sequence (F._{sol}.viral Fig 2b) contained suboptimal codon usage for expression in mammalian cells. In addition, a possible eight 3' splice sites were identified, including preceding lariat sequences at four positions. Poly (A) adenylation sites (AATAAA <400>570) were also identified at 4 positions. In addition, the F natural sequence like the viral sequence is approximately 65% AT rich. Most mammalian expressed genes are less than 50% AT rich. The DNA sequence encoding the transmembrane form of RSV F is also shown in Fig 2a.

15

In an attempt to overcome poor expression levels in mammalian cells, a new F sequence was designed that:

- (a) retained the same encoded amino acid sequence
 - 20 (b) used wherever possible optimum codon usage
 - (c) removed all potential splice sites and poly A sites
 - (d) removed as many CG doublets as these may be methylation sites
 - (e) designed unique restriction sites to allow cassette mutagenesis
 - (f) sequence was checked by secondary structure and any large hairpin loops were
- 25 destabilised by changing the sequence

Sequences encoding a transmembrane version of F and the F_{sol} protein are shown in Fig.3a and 3b respectively.

- 30 Both of these optimised sequences F.opt and F._{sol}.opt are compared to the viral sequence in Figs 2a and 2b.

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The synthetic DNA sequence Fopt (also referred to as F_{sol}.opt) was assembled and cloned as outlined in Fig. 4a and 4b. In brief, single stranded synthetic DNA fragments of average length 60 bases were annealed and ligated together to produce three fragments

- 5 (1) a 631bp Pst I-Mfe I fragment
- (2) a 606bp Mfe I-Xho I fragment
- (3) a 379bp Xho I-Bam HI fragment.

These gel purified fragments were cloned in pLitmus 38 or a derivative of pLITMUS 10 (pLITMUS 273/279). Clones containing the correct sequence were used as a DNA source to assemble the full length gene as outlined in Fig. 4b. In brief the respective fragment Pst-Mfe I, Xho I-Bam HI and Mfe-Xho I were sequentially cloned into the CMV expression vector pCICO or its derivatives. [pCICO is a derivative of pJW4304 which contains a full length CMV promoter and the CMV authentic intron sequence preceding the Pst I site. 15 The 3' terminator used is derived from SV40 early region and this vector also contains the SV40 origin of replication. The plasmid is from the pUC series and contains an ampicillin-resistance gene. (pJW4304 was obtained from J. Mullins Dept. of Microbiology, University of Washington, Chapman *et al.*, NAR, 19:3979-3980, 1991)]. This produced the final clone pCICO.Fopt.

20 pCICO.Fopt was further modified by cloning in a 270bp EcoRI-Xba I fragment (see Fig. 4b) which encodes the transmembrane and cytoplasmic domains of the RSV F protein. Again, the DNA sequence was optimised as for the soluble version See Fig. 2b for comparison of F.opt (Fopt FL sequence) and F (viral with a few additional restriction site changes) and F.viral (viral sequence). The resulting CMV expression plasmid is called 25 pCICO.F.FL.opt. Note FL stands for the term full length and refers to a form of F that includes the transmembrane region and the cytoplasmic tail.

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EXAMPLE 2
IN VITRO EXPRESSION OF RSV F EXPRESSION

Vectors pCICO containing the F_{sol}.opt sequence (pCICO.Fopt) and the F_{sol} sequence 5 (pCICO.FS3) were tested for expression by CaPO₄ precipitation in 293 cells. Cells in a 60ml dish were transfected with 5µg of plasmid and 0.5µg of pVARNA. Cells were radioactively labelled with ³⁵S methionine and ³⁵S cysteine 24 hours post transfection and the supernatants collected 5 hours after labelling. Supernatants were immunoprecipitated with a RSV F specific monoclonal antibody and the precipitates were analysed by 10 polyacrylamide gel electrophoresis. Gels were subjected to fluorography, dried and exposed to X-ray film. Fig. 5 shows an autoradiograph comparing the amount of F in pCICO.FS3, pCICO.Fopt and control (mock-transfected) cells. Expression is much improved in the pCICO.Fopt transfected cells by at least 20 fold.

15

EXAMPLE 3
RSV FUSION ASSAY

293 cells were also transfected with the plasmid pCICO.F.FL.opt which contains the transmembrane spanning version of F. Cells transfected with this plasmid were observed 20 24-48 hours post transfection to contain many large syncitia and dying cells. Control cells were confluent. The F transfected cells look indistinguishable from RSV infected cells. Thus high level expression of F is all that is necessary for cell fusion to occur. This is markedly different to what is reported in the literature (Collins et al, Fields, and references within). This assay forms a useful screen for detecting F specific inhibitors of RSV fusion. 25 Agents found by this assay are also useful for inhibiting RSV replication.

EXAMPLE 4
RSV SECOND CLEAVAGE SITE MUTANTS

30 The RSV F protein sequence at amino acid singular numbers 106-109, contains the sequence RARR. As shown in Figure 1c, this potential cleavage site is contained within

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the F2 sub-unit of the F protein. When the F protein is expressed in mammalian cells, proteolytic cleavage occurs at two sites being site 1 (KKRKRR amino acids 131-136) which was previously identified and the previously unknown site 2 (RARR amino acids 106-109).

5

The site RARR was mutated to GQGR in the expression plasmid pCICO.FL.Fopt to give rise to the plasmid pCICO.F.FL.S2-2. Transfection of this plasmid into 293 cells revealed cleavage at site 1 but not at site 2 as expected. This was detected by a larger size F2 sub-unit (~30K versus 18K) in the S2-2 mutant than in the wild type. The size of the protein
10 between site 2 and site 1 would be expected to be 10-12K (25 amino acids plus two NH₂ – linked glycosylation sites). It was surprisingly noted that no evidence of fusion was seen in the 293 cells transfected with the S2-2 mutant plasmid of wild type. This evidence would suggest that cleavage at both site 1 and site 2 is necessary for cleavage. Note that in additional experiments, mutation of site 1 (KKRKRR) to GGKQGR, produced a mutant
15 showing no fusion activity.

In the next experiments the issue of whether the sequence between sites 1 and 2 were necessary for fusion was addressed. A mutant was constructed by standard techniques (cassette mutagenesis) in which amino acids 106-130 were deleted. This mutant is
20 designated delta 106-130. Transfection of 293 cells with an expression plasmid containing this mutant (pCICO.FLFΔ106-130) showed that fusion did occur. This fusion was phenotypically different from wild type in that only small syncytia were visible, suggesting that the ability of the RSV F protein to initiate or perform fusion had been attenuated.

25

EXAMPLE 5
EXPRESSION OF NATURAL F -V- F OPTIMISED SEQUENCE

5 *Cloning of RSVA2 F cDNA*

RNA prepared from RSVA2 infected Hep-2 cells was used as a source of RSV A2 F mRNA. RT-PCR (reverse transcriptase PCR) using 5'- and 3'- end primers was used to prepare cDNA encoding RSV A2 F according to standard methods. PCR products were 10 subcloned into standard vectors. Sequencing of many clones revealed a consensus sequence for the F gene of RSV A2. This sequence is shown in Figure 6 as F.nat and compared to F.viral. The F.nat sequence differs at nt 174 and 222. Both of these T to C changes do not result in amino acid changes. A pCICO vector containing the F.nat sequence (called pCICO.F.nat) was assembled from a synthetic Pst1 to Acc1 157 bp 15 fragment ligated to a 445 bp Acc1 to Mfe 1 fragment and a 1125 bp Mfe 1 to Xba 1 fragment derived from independent RT-PCR RSVA2 F cDNA clones. The synthetic fragment was used to make the addition of extra 5'-untranslated sequences not present in the PCR products. The 5'-untranslated sequence is 5'- CTGCAGTCACCGTCTTGA-CACC -3' (<400>571) and includes a Pst 1 site. This sequence is added just 5' to the 20 initiator ATG in the following constructions pCICO.F.nat and the previously described pCICO.F.FL.opt. The Acc1 to Mfe 1 and Mfe 1 to Xba1 fragments were derived from independent RT-PCR RSVA2 F cDNA clones. The sequence F.nat encodes the same 574 amino acid sequence as shown in Fig 1.

25 *Expression of pCICO.F.FL.opt versus pCICO.F.nat*

293 cells were transfected with plasmids pCICO.F.FL.opt , pCICO.F.nat and a control as described in example 2. Cells were harvested at 24, 48 and 72 hours post transfection in cell lysis buffer. The amount of F protein in these samples was measured by Western blot 30 analysis using standard techniques. The primary antibody called 18B2, is a mouse monoclonal antibody that recognizes the F1 protein. A proteolytic breakdown product of

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F1 called F1' is also recognized by this antibody. The western blots were developed using a secondary anti - mouse horseradish peroxidase antibody and a light emitting substrate according to standard procedures.

- 5 The results of these experiments are shown in fig 7. Lanes labelled WT refer to samples from cells transfected with pCICO.F.FL.opt : A2 lanes refer to samples from cells transfected with pCICO.F.nat and Ctrl lanes are from cells transfected with control plasmids lacking either F sequence. F protein (F1 and F1') is only observed in WT lanes indicating that the F expression level in cells transfected with pCICO.F.FL.opt is far
10 superior to those transfected with pCICO.F.nat.

In parallel to the above experiments 293 cells were transfected with the same three plasmids and observed microscopically for signs of cell to cell fusion (syncytia formation).
15 In three parallel experiments only cells tranfected with pCICO.F.FL.opt show any cell to syncytia in pCICO.FL.opt transfected cells. No fusion is observed in either the pCICO.F.nat or Ctrl transfected cells (see Fig 8).

Those skilled in the art will appreciate that the invention described herein is susceptible to
20 variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

TNIMITTIII <400>511	NIMMITTIIIV <400>512
IMITTIIIVI <400>513	MITTIIIVII <400>514
ITIIIVIIV <400>515	TTIIIVIIVI <400>516
TIIIVIIVIL <400>517	IIIIVIIVILL <400>518
IIIVIIVILLS <400>519	IVIIVIIVSSL <400>520
VIVIVILLSLI <400>521	IIVIVILLSLIA <400>522
IVILLSLIAV <400>523	VILLSLIAVG <400>524
ILSLIHAVGL <400>525	LLSLIHAVGLL <400>526
LSLIAVGLLL <400>527	SLIAVGLLLY <400>528
LIAVGLLLKC <400>529	IAVGLLLYCK <400>530
AVGLLLYCKA <400>531	VGLLLYCKAR <400>532
GLLLYCKARS <400>533	LLLYCKARST <400>534
LLYCKARSTP <400>535	LYCKARSTPV <400>536
YCKARSTPVT <400>537	CKARSTPVTL <400>538
KARSTPVTLS <400>539	ARSTPVTLSK <400>540
RSTPVTLSKD <400>541	STPVTLSKDQ <400>542
TPVTLSDQL <400>543	PVTLSDQLS <400>544
VTLSKDQLSG <400>545	TLSKDQLSGI <400>546
LSKDQLSGIN <400>547	SKDQLSGINN <400>548
KDQLSGINNI <400>549	DQLSGINNIA <400>550
QLSGINNIAF <400>551	LSGINNIAFS <400>552
SGINNIAFSN <400>553	

43. The agent according to claim 42 wherein said antagonist interacts with a sequence selected from <400>88, <400>89, <400>90, <400>91, <400>92, <400>93 or <400>94.

44. A viral F protein variant comprising a mutation in the intervening peptide sequence wherein said variant exhibits modulated functional activity relative to wild-type F protein or a derivative, homologue, analogue, chemical equivalent or mimetic of said variant.

45. The variant according to claim 44 wherein said variant exhibits down-regulated functional activity relative to wild-type F protein.

46. The variant according to claim 44 or claim 45 wherein said virus is a virus from the family Paramyxoviridae.

47. The variant according to claim 46 wherein said virus is of the sub-family Pneumovirinae.

48. The variant according to claim 47 wherein said virus is respiratory syncytial virus.

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49. The variant according to claim 48 wherein said variant comprises a mutation in the cleavage site defined by amino acids RARR (<400>564).

50. The variant according to claim 49 wherein said mutation comprises one or more of the amino acid substitutions selected from the following list:

- (i) R106G
- (ii) A107Q
- (iii) R108G.

51. The variant according to claim 50 wherein said variant comprises the sequence substantially as set forth in <400>565.

52. The variant according to any one of claims 44-48 wherein said variant comprises a multiple amino acid deletion from the intervening peptide sequence.

53. The variant according to claim 52 wherein said amino acid deletion is a partial deletion of the intervening peptide sequence.

54. The variant according to claim 53 wherein said deletion is a deletion of the peptide sequence

RARRELPRFMNYTLNNAKKTNVTLS <400>569

55. The variant according to claim 54 wherein said variant comprises the amino acid sequence substantially as set forth in <400>567.

56. An isolated nucleic acid molecule selected from the list consisting of:

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- (i) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a mutation in the intervening peptide sequence wherein said variant exhibits modulated functional activity relative to wild-type F protein.
- (ii) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a mutation in the intervening peptide sequence wherein said variant exhibits down-regulated functional activity relative to wild-type F protein.
- (iii) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a respiratory syncytial virus F protein or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a mutation in the cleavage site defined by amino acids RARR wherein said variant exhibits down-regulated functional activity relative to wild-type F protein.
- (iv) An isolated nucleic acid molecule or derivative or equivalent thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a respiratory syncytial virus F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises one or more of the amino acid substitutions selected from the following list:

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- (a) R106G
- (b) A107Q
- (c) R108G

- (v) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a multiple amino acid deletion from the intervening peptide sequence wherein said variant exhibits down-regulated functional activity relative to wild-type F protein.
- (vi) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises a partial deletion of the intervening peptide sequence and more preferably a deletion of the peptide sequence

RARRELPRFMNYTLNNAKKTNVTLS <400>569.

- (vii) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue, analogue, chemical equivalent or mimetic of said variant, which variant comprises the amino acid sequence substantially as set forth in <400>567.
- (viii) An isolated nucleic acid molecule or derivative or analogue thereof comprising a nucleotide sequence encoding or complementary to a sequence encoding a viral F protein variant or derivative, homologue,

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analogue, chemical equivalent or mimetic of said variant, which variant comprises the amino acid sequence substantially as set forth in <400>565.

- (ix) An isolated nucleic acid molecule or derivative or analogue thereof comprising the nucleotide substantially as set forth in <400>568.
- (x) An isolated nucleic acid molecule or derivative or analogue thereof comprising the nucleotide substantially as set forth in <400>566.

57. The isolated nucleic acid molecule of claim 56 wherein said virus is a virus from the family Paramyxoviridae.

58. The isolated nucleic acid molecule of claim 57 wherein said virus is of the subfamily Pneumovirinae.

59. The isolated nucleic acid molecule of claim 58 wherein said virus is respiratory syncytial virus.

60. A recombinant viral construct comprising a nucleic acid molecule encoding a viral F protein or derivative thereof, the nucleotide sequence of which nucleic acid molecule comprises codons optimised for expression in a eukaryotic cell, wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein.

61. A recombinant viral construct comprising a nucleic acid molecule encoding a viral F protein variant or derivative thereof wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein variant.

62. A vaccine comprising a recombinant viral construct which construct comprises a nucleic acid molecule encoding a respiratory syncytial virus F protein or derivative thereof,

the nucleic sequence of which nucleic acid molecule is optimised for expression in a eukaryotic cell wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein.

63. A vaccine comprising a recombinant viral construct which construct comprises a nucleic acid molecule encoding a respiratory syncytial virus F protein variant or derivative thereof, wherein said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said F protein variant.

64. A vaccine according to claim 62 or claim 63 wherein said nucleotide sequence is defined in one of <400>5, <400>6, <400>566 or <400>568.

65. Use of the agent according to any one of claims 41-43 or identified in accordance with the method of any one of claims 34-40 to modulate F protein functional activity.

66. Use of the agent according to any one of claims 41-43 or identified in accordance with the method of any one of claims 34-40 in the therapeutic and/or prophylactic treatment of conditions characterised by infection with a negative sense single stranded RNA virus.

67. A method of modulating at least one functional activity associated with a viral F protein in a subject, said method comprising introducing into said subject an effective amount of a F protein modulatory agent according to any one of claims 41-43 or identified in accordance with the method of any one of claims 34-40 for a time and under conditions sufficient for said agent to interact with said F protein.

68. The method according to claim 68 wherein said functional activity is F protein mediated host cell virion fusion and/or virion budding and said modulating is down-regulation.

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69. A method of modulating at least one functional activity associated with a viral F protein, said method comprising contacting said viral F protein with an effective amount of a F protein modulatory agent according to any one of claims 41-43 or identified in accordance with the method of any one of claims 34-40 for a time and under conditions sufficient for said agent to interact with said F protein.

70. A method for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus in a subject, said method comprising administering to said subject an effective amount of an agent according to any one of claims 41-43 or identified in accordance with the method of any one of claims 34-40 which agent is capable of down-regulating at least one functional activity of the F protein expressed by said virus, for a time and under conditions sufficient for said agent to interact with said F protein.

71. A method for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded virus in a subject, said method comprising administering to said subject an effective amount of a composition comprising an F protein or derivative thereof, F protein variant or derivative thereof and/or a nucleic acid molecule encoding said F protein or F protein variant or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein or nucleic acid molecule for a time and under conditions sufficient for said composition to down regulate said viral F protein functional activity.

72. The method according to claim 71 wherein said subject is a mammal.

73. The method according to claim 72 wherein said mammal is a human.

74. Use of an agent capable of modulating at least one functional activity of a viral F protein which agent according to any one of claims 41-43 or identified in accordance with the method of any one of claims 34-40 in the manufacture of a medicament for the treatment and/or prophylaxis of a condition characterised by infection with negative sense

single stranded RNA virus.

75. Use of a composition comprising an F protein or derivative thereof, F protein variant or derivative thereof, nucleic acid molecule encoding said F protein or F protein variant according to any one of claims 41-43 or identified in accordance with the method of any one of claims 34-40 or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein or nucleic acid molecule, in the manufacture of a medicament for the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus.

76. Use of an agent, which agent, according to any one of claims 41-43 or identified in accordance with the method of any one of claims 34-40 in the manufacture of a medicament for the modulation of at least one viral F protein associated functional activity.

77. Agents for use in modulating the functional activity of a viral F protein wherein said agent is identified in accordance with the method of any one of claims 34-40.

78. Agents for use in the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus wherein said agent is identified in accordance with the methods of any one of claims 34-40.

79. A composition comprising an F protein or derivative thereof, F protein variant or derivative thereof, a nucleic acid molecule encoding said F protein or F protein variant or a derivative, homologue, analogue, chemical equivalent or mimetic of said protein or nucleic acid molecule for use in the treatment and/or prophylaxis of a condition characterised by infection with a negative sense single stranded RNA virus.

1 / 40

70 140 210 280 350 420 490 560 574

Figure 1a

2/40

MELLILKANAITTILTAVTECFAASGQNITEEFYQOSTCSAVSKGYLSALRTGMYTSVITIELSNIKKNKCN
70
GTDAAKVKLIIKQELDKYKNAVTTELQLLMOSTQATNNRARELPREMNYTLLNAKKTNVTLSKKRKKRFLGF
140
LLGVGSAAASGVAVSKVLHLEGEVNKIKSALLSTNKAVVSLSGVSVLTSKVLDLKNYIDKQLLPIVNKQ
210
SCSISNIETVIEFQQKNNRLLITREFSVNAGVTPVSTYMLTNSELLSLINDMPIITNDQKKLMSNNVQI
280
VRQQSYSIMSIIKEEVLAYVYVQLPLYGVIDTPCWKLHTSPLCTNTKEGSNICLRTDRGWYCDNAGSVS
350
FFPQAETCKVQSNRVFCDTMNSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSVITSLGAI VSCYGKT
420
KCTASNKNRGIIKTFSNGCDYVSINKGVDTVSVGNTLYYVNKQEGKSLYVKGEPIINFYDPLVFPSDEFDA
490
SISQVNEKINQSLAFIRKSDELLHNVNAGKSTTN
524

Figure 1b

3/40

F and F_{sol} forms of the RSV fusion Protein

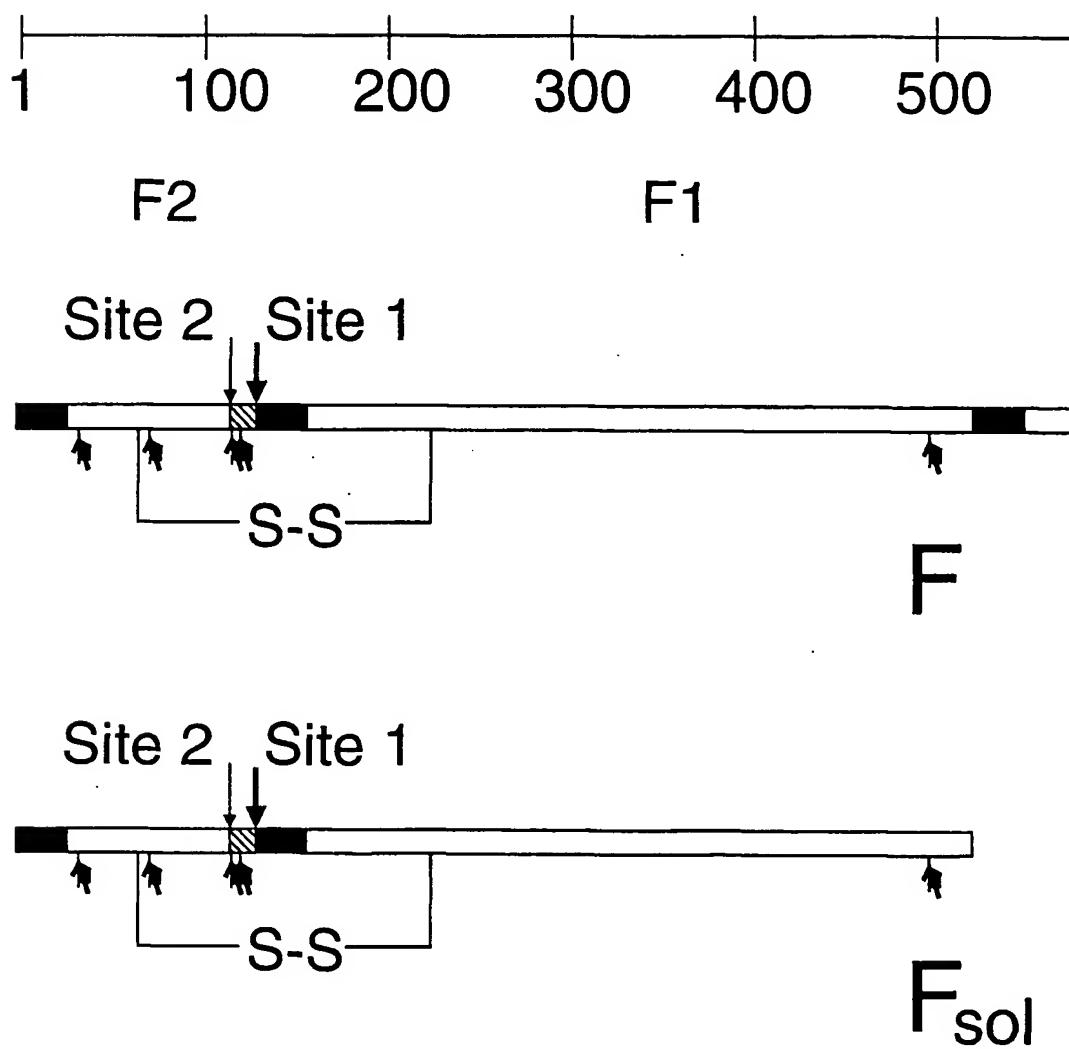


Figure 1c
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4/40

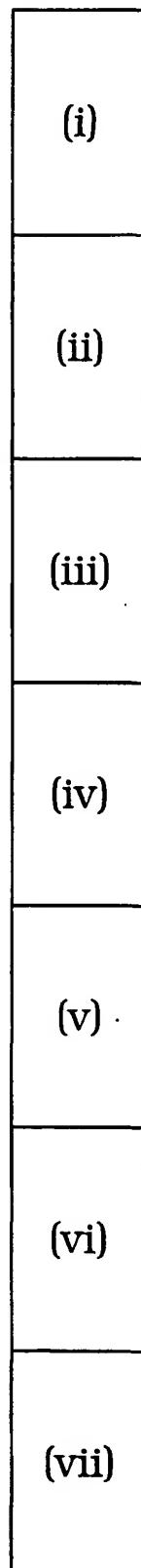


Figure 2a
SUBSTITUTE SHEET (RULE 26)

5/40

ClustalW Formatted Alignments

	10	20	30	
<i>F.viral</i>	ATGGAGTTGCTAATCCTCAAAAGCAAATGCA			
<i>F</i>	ATGGAGTTGCTAATCCTCAAAAGCAAATGCA			
<i>F.opt</i>	ATGGAGCTGCTGATCCTGAAGGCCAACGCC			
	ATGGAGTTGCTAATCCTCAAAAGCAAATGCA			
		40	50	60
<i>F.viral</i>	ATTACCCACAATCCTCACTGCAGTCACATT			
<i>F</i>	ATTACCCACAATCCTCACTGCAGTCACATT			
<i>F.opt</i>	ATCACCCACCATCCTGACCGCGGTGACCTTC			
	ATTACCCACAATCCTCACTGCAGTCACATT			
		70	80	90
<i>F.viral</i>	TGTTTTGCTTCTGGTCAAAACATCACTGAA			
<i>F</i>	TGTTTTGCTTCTGGTCAAAACATCACTGAA			
<i>F.opt</i>	TGCTTCGGCTCTGGCAGAACATCACTGAG			
	TGTTTTGCTTCTGGTCAAAACATCACTGAA			
		100	110	120
<i>F.viral</i>	GAATTTTATCAATCAACATGCAGTGCAAGTT			
<i>F</i>	GAATTTTATCAATCAACATGCAGTGCAAGTT			
<i>F.opt</i>	GAGTCTAACCGAGAGCACTTGTCCGCTGTG			
	GAATTTTATCAATCAACATGCAGTGCAAGTT			
		130	140	150
<i>F.viral</i>	AGCAAAAGGCTATCTTAGTGCTCTGAGAAC			
<i>F</i>	AGCAAAAGGATATCTTAGTGCTCTGAGAAC			
<i>F.opt</i>	AGCAAGGGCTACCTGAGCGCCCTGAGGACC			
	AGCAAAAGGCTATCTTAGTGCTCTGAGAAC			
		160	170	180
<i>F.viral</i>	GGTTGGTATACCAAGTGTATAACTATAGAA			
<i>F</i>	GGTTGGTATACCAAGTGTATAACTATAGAA			
<i>F.opt</i>	GGTTGGTACACCCAGCGT GATCACCCATCGAG			
	GGTTGGTATACCAAGTGTATAACTATAGAA			
		190	200	210
<i>F.viral</i>	TTAAGTAATATCAAGAAAAATAAGTGTAAT			
<i>F</i>	TTAAGTAATATCAAGAAAAATAAGTGTAAT			
<i>F.opt</i>	CTGAGCAACATCAAGAAGAACAAAGTGCAAC			
	TTAAGTAATATCAAGAAAAATAAGTGTAAT			
		220	230	240
<i>F.viral</i>	GGAACACAGATGCTAAGGTAAAATTGATAAAA			
<i>F</i>	GGTACCGATGCTAAGGTAAAATTGATAAAA			
<i>F.opt</i>	GGCACCGACGCCAAGGTGAAGCTGATCAAG			
	GGACCGATGCTAAGGTAAAATTGATAAAA			

Figure 2a(i)

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	250	260	270
<i>F.viral</i>	CAAGAATTAGATAAAATATAAAAAATGCTGTA		
<i>F</i>	CAAGAATTAGATAAAATATAAAAAATGCTGTA		
<i>F.opt</i>	CAAGAGCTGGACAAGTACAAAGAACGCCGTG CAAGAATTAGATAAAATATAAAAAATGCTGTA		
	280	290	300
<i>F.viral</i>	ACAGAATTGCAGTTGCTCATGCAAAGCACA		
<i>F</i>	ACAGAATTGCAGTTGCTCATGCAGTCGACA		
<i>F.opt</i>	ACCGAGCTGCAACTGCTGATGCAGTCGACT ACAGAATTGCAGTTGCTCATGCAGTCGACA		
	310	320	330
<i>F.viral</i>	CAAGCAACAAACAATCGAGGCCAGAAGAGAA		
<i>F</i>	CAAGCAACAAACAATCGAGGCCAGAAGAGAA		
<i>F.opt</i>	CAAGCCACCAACAACAGAGCCCCGAGAGAG CAAGCAACAAACAATCGAGGCCAGAAGAGAA		
	340	350	360
<i>F.viral</i>	CTACCAAGGTTATGAATTATACACTCAAC		
<i>F</i>	CTACCTAGGTTATGAATTATACACTCAAC		
<i>F.opt</i>	CTGCCCGCTTCAATGAACCTACACCCCTGAAC CTACC AGGTTATGAATTATACACTCAAC		
	370	380	390
<i>F.viral</i>	AATGCCAAAAAAACCAAATGTAACATTAAAGC		
<i>F</i>	AATGCCAAAAAAACCAAATGTAACACTTTTCG		
<i>F.opt</i>	AACGCCAAGAACCAACCGTGACCCCTGTCCC AATGCCAAAAAAACCAAATGTAACACT TCC		
	400	410	420
<i>F.viral</i>	AAGAAAAGGAAAAGAAGATTCTTGGTTTT		
<i>F</i>	AAGAAAAGGAAAAGAAGATTCTTGGTTTT		
<i>F.opt</i>	AAGAAAGAGGAAGCGCCGCTTCCCTGGGCTTC AAGAAAAGGAAAAGAAGATTCTTGGTTTT		
	430	440	450
<i>F.viral</i>	TTGTTAGGTGTTGGATCTGCAATCGCCAGT		
<i>F</i>	TTGTTAGGTGTTGGATCCGCAATCGCCAGT		
<i>F.opt</i>	CTGCTGGCGTGGCTCCGCCATTGCCAGT TTGTTAGGTGTTGGATCCGCAATCGCCAGT		
	460	470	480
<i>F.viral</i>	GGCGTTGCTGTATCTAACAGGTCCTGCACCTA		
<i>F</i>	GGCGTTGCTGTATCTAACAGGTCCTGCATCTA		
<i>F.opt</i>	GGCGTGGCGTGTCCAAAGGTGCTGCACCTG GGCGTTGCTGTATCTAACAGGTCCTGCACCTA		
	490	500	510
<i>F.viral</i>	GAAGGGGAAGTGAACAAAGATCAAAAGTGC		
<i>F</i>	GAAGGGGAAGTGAACAAAGATCAAAAGTGC		
<i>F.opt</i>	GAGGGCGAGGTGAACAAAGATCAAGAGTGC GAGGGGGAAAGTGAACAAAGATCAAAAGTGC		

Figure 2a(ii)

SUBSTITUTE SHEET (RULE 26)

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	520	530	540
<i>F.viral</i>	CTACTATCCACAAACAAAGGCTGTAGTCAGC		
<i>F</i>	CTACTATCCACAAACAAAGGCTGTAGTCAGC		
<i>F.opt</i>	CTGCTGTCCACATAACAAGGCCGTGGTGAGC		
	CTACTATCCACAAACAAAGGCTGTAGTCAGC		
	550	560	570
<i>F.viral</i>	TTATCAAAATGGAGTTAGTGTCTTAACCAGC		
<i>F</i>	TTATCAAAATGGAGTTAGTGTCTTAACCAGC		
<i>F.opt</i>	CTGAGCAACGGCGTGAAGTAGTGTGCTGACTAGC		
	TTATCAAAATGGAGTTAGTGTCTTAACCAGC		
	580	590	600
<i>F.viral</i>	AAAGTGTAGACCTCAAAAAACTATATAGAT		
<i>F</i>	AAAGTGTAGACCTCAAAAAACTATATAGAT		
<i>F.opt</i>	AAGGTGCTGGACCTGAAGAACTACATCGAC		
	AAAGTGTAGACCTCAAAAAACTATATAGAT		
	610	620	630
<i>F.viral</i>	AAAACAATTGTTACCTATTGTGAACAAGCAA		
<i>F</i>	AAAACAATTGTTACCTATTGTGAACAAGCAA		
<i>F.opt</i>	AAAGCAATTGCTGCCATCGTAGAACAGGAG		
	AAAACAATTGTTACCTATTGTGAACAAGCAA		
	640	650	660
<i>F.viral</i>	AGCTGCAGCATATCAAATATAGAAACTGTG		
<i>F</i>	AGCTGCAGCATATCAAATATAGAAACTGTG		
<i>F.opt</i>	TCCCTGTAGCATCTCCAACATCGAGACTGTG		
	AGCTGCAGCATATCAAATATAGAAACTGTG		
	670	680	690
<i>F.viral</i>	ATAGAGTTCCAACAAAGAACAAACAGACTA		
<i>F</i>	ATAGAGTTCCAACAAAGAACAAACAGACTA		
<i>F.opt</i>	ATCGAGTTCCAGCAGAACAAACCGCCTG		
	ATAGAGTTCCAACAAAGAACAAACAGACTA		
	700	710	720
<i>F.viral</i>	CTAGAGATTACCAAGGGAATTAGTGTAAAT		
<i>F</i>	CTAGAGATTACCAAGGGAATTAGTGTAAAT		
<i>F.opt</i>	CTGGAAATCACCCGGGAGTTCAAGTGTGAAAC		
	CTAGAGATTACCAAGGGAATTAGTGTAAAT		
	730	740	750
<i>F.viral</i>	GCAGGTTGTAACACTACACCTGTAAAGCACTTAC		
<i>F</i>	GCAGGTTGTAACACTACACCTGTAAAGCACTTAC		
<i>F.opt</i>	GCTGGCGTGAACCACTCCGTCTCCACCTAC		
	GCAGGTTGTAACACTACACCTGTAAAGCACTTAC		
	760	770	780
<i>F.viral</i>	ATGTTAACTAATAGTGAATTATGTCAATT		
<i>F</i>	ATGTTAACTAATAGTGAATTATGTCAATT		
<i>F.opt</i>	ATGCTGACCAACAGCGAGCTGCTGAGCCTG		
	ATGTTAACTAATAGTGAATTATGTCAATT		

Figure 2a(iii)

SUBSTITUTE SHEET (RULE 26)

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	790	800	810
<i>F.viral</i>	AT C A A T G A T A T G C C T A T A A C A A A T G A T C A G		
<i>F</i>	AT C A A T G A T A T G C C T A T A A C A A A T G A T C A G		
<i>F.opt</i>	AT C A A C G A C A T G C C C A T C A C C A A C G A C C A G		
	AT C A A T G A T A T G C C T A T A A C A A A T G A T C A G		
	820	830	840
<i>F.viral</i>	A A A A A G T T A A T G T C C A A C A A T G T T C A A A T A		
<i>F</i>	A A A A A G T T A A T G T C C A A C A A T G T T C A A A T A		
<i>F.opt</i>	A A G A A G C T T A T G T C C A A C A A C G T G C A G A T C		
	A A A A A G T T A A T G T C C A A C A A T G T T C A A A T A		
	850	860	870
<i>F.viral</i>	G T T A G A C A G C A A A G T T A C T C T A T C A T G T C C		
<i>F</i>	G T T A G A C A G C A A A G T T A C T C T A T C A T G T C C		
<i>F.opt</i>	G T G A G G C A G C C A G A G C T A C T C C A T C A T G A G C		
	G T T A G A C A G C A A A G T T A C T C T A T C A T G T C C		
	880	890	900
<i>F.viral</i>	A T A A T A A A A G A G G A A G T C T T A G C A T A T G T A		
<i>F</i>	A T A A T A A A A G A G G A A G T C T T A G C A T A T G T A		
<i>F.opt</i>	A T C A T C A A G G A G G G A G I G T G C T G G C C T A T G T G		
	A T A A T A A A A G A G G A A G T C T T A G C A T A T G T A		
	910	920	930
<i>F.viral</i>	G T A C A A T T A C C A C T A T A T G G T G T T A T A G A T		
<i>F</i>	G T A C A A T T A C C A C T A T A T G G T G T T A T A G A T		
<i>F.opt</i>	G T G C A G C T G C C C C T G T A C G G C G T C A T C G A T		
	G T A C A A T T A C C A C T A T A T G G T G T T A T A G A T		
	940	950	960
<i>F.viral</i>	A C A C C C T G T T G G A A A C T A C A C A C A T C C C C T		
<i>F</i>	A C A C C C T G T T G G A A A C T A C A C A C A T C C C C T		
<i>F.opt</i>	A C C C C T T G C T G G A A G C T G C A C A C C A G C C C C		
	A C A C C C T G T T G G A A A C T A C A C A C A T C C C C T		
	970	980	990
<i>F.viral</i>	C T A T G T A C A A C C A A C A C A A A A G A A G G G T C C		
<i>F</i>	C T A T G T A C A A C C A A C A C A A A A G A A G G G T C C		
<i>F.opt</i>	C T G T G C A C C A C C A A C A C C A A G G A A G G G C A G C		
	C T A T G T A C A A C C A A C A C A A A A G A A G G G T C C		
	1000	1010	1020
<i>F.viral</i>	A A C A T C T G T T T A A C A A G A A C T G A C A G A G G A		
<i>F</i>	A A C A T C T G T T T A A C A A G A A C T G A C A G A G G A		
<i>F.opt</i>	A A C A T C T G C C T G A C C C G G A C C G A C C G C G G C		
	A A C A T C T G T T T A A C A A G A A C T G A C A G A G G A		
	1030	1040	1050
<i>F.viral</i>	T G G T A C T G T G A C A A T G C A G G A T C A G T A T C T		
<i>F</i>	T G G T A C T G T G A C A A T G C A G G A T C A G T A T C T		
<i>F.opt</i>	T G G T A C T G T G A C A A C G C T G G C T C G G T G A G C		
	T G G T A C T G T G A C A A T G C A G G A T C A G T A T C T		

Figure 2a(iv)

SUBSTITUTE SHEET (RULE 26)

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	1060	1070	1080
<i>F.viral</i>	TTCTTCCCACAAGCTGAAACATGTAAGTT		
<i>F</i>	TTCTTCCCACAAGCTGAAACATGTAAGTT		
<i>F.opt</i>	TTCTTCCCCTCAAGCTGAAACCTGCAAGGTC		
	TTCTTCCCACAAGCTGAAACATGTAAGTT		
	1090	1100	1110
<i>F.viral</i>	CAATCAAATCGAGTATT TTGTGACACAATG		
<i>F</i>	CAATCAAATCGAGTATT TTGTGACACAATG		
<i>F.opt</i>	CAGAGCAACAGAGTGTCTGTGACACCATG		
	CAATCAAATCGAGTATT TTGTGACACAATG		
	1120	1130	1140
<i>F.viral</i>	AACAGTTAACATTACCAAGTGAAGTAAAT		
<i>F</i>	AACAGTTAACATTACCAAGTGAAGTAAAT		
<i>F.opt</i>	AACTCCCTGACCCCTGCCCTCCGAGGTGAAC		
	AACAGTTAACATTACCAAGTGAAGTAAAT		
	1150	1160	1170
<i>F.viral</i>	CTCTGCAATGTTGACATAATTCAACCCCCAAA		
<i>F</i>	CTCTGCAATGTTGACATAATTCAACCCCCAAA		
<i>F.opt</i>	CTGTGCAACCGTGGATATCTTCAACCCCCAAG		
	CTCTGCAATGTTGACATAATTCAACCCCCAAA		
	1180	1190	1200
<i>F.viral</i>	TATGATTGTAAAAATTATGACTTCAAAAAACA		
<i>F</i>	TATGATTGTAAAAATTATGACTTCAAAAAACA		
<i>F.opt</i>	TATGACTGCAAGATCATGACCTCCCAAGACC		
	TATGATTGTAAAAATTATGACTTCAAAAAACA		
	1210	1220	1230
<i>F.viral</i>	GATGTAAGCAGCTCCGTTATCACATCTCTA		
<i>F</i>	GATGTAAGCAGCTCCGTTATCACATCTCTA		
<i>F.opt</i>	GATGTCCTCGAGCTCCGTTATCACATCTCTG		
	GATGTAAGCAGCTCCGTTATCACATCTCTA		
	1240	1250	1260
<i>F.viral</i>	GGAGCCATTGTTGTCATGCTATGGCAAAACT		
<i>F</i>	GGAGCCATTGTTGTCATGCTATGGCAAAACT		
<i>F.opt</i>	GGCGCCATCGTGTCCCTGCTATGGCAAGACC		
	GGAGCCATTGTTGTCATGCTATGGCAAAACT		
	1270	1280	1290
<i>F.viral</i>	AAATGTACAGCATCCAATAAAAAATCGTGG		
<i>F</i>	AAATGTACAGCATCCAATAAAAAATCGTGG		
<i>F.opt</i>	AAGTGCACCGGCAGCAACAAAGAACCGGGGG		
	AAATGTACAGCATCCAATAAAAAATCGTGG		
	1300	1310	1320
<i>F.viral</i>	ATCATAAAGACATTCTAACGGGTGCGAT		
<i>F</i>	ATCATAAAGACATTCTAACGGGTGCGAT		
<i>F.opt</i>	ATCATCAAGACCTTCAGCAATGGGTGCGAC		
	ATCATAAAGACATTCTAACGGGTGCGAT		

Figure 2a(v)

SUBSTITUTE SHEET (RULE 26)

10/40

	1330	1340	1350
<i>F.viral</i>	T A T G T A T C A A A T A A A G G G G T G G A C A C T G T G		
<i>F</i>	T A T G T A T C A A A T A A A G G G G T G G A C A C T G T G		
<i>F.opt</i>	T A C G T T T C G A A C A A G G G C G T G G A C A C T G T G T A T G T A T C A A A T A A A G G G G T G G A C A C T G T G		
	1360	1370	1380
<i>F.viral</i>	T C T G T A G G T A A C A C A T T A T A T T A T G T A A A T		
<i>F</i>	T C T G T A G G T A A C A C A T T A T A T T A T G T A A A T		
<i>F.opt</i>	T C C G T G G G C A A C A C C C T G T A C T A C G T G A A C T C T G T A G G T A A C A C A T T A T A T T A T G T A A A T		
	1390	1400	1410
<i>F.viral</i>	A A G C A A G A A G G T A A A A G T C T C T A T G T A A A A		
<i>F</i>	A A G C A A G A A G G T A A A A G T C T C T A T G T A A A A		
<i>F.opt</i>	A A G C A A G A A G G G C A A G A G C T G T A T G T G A A G A A G C A A G A A G G T A A A A G T C T C T A T G T A A A A		
	1420	1430	1440
<i>F.viral</i>	G G T G A A C C A A T A A T A A A T T T C T A T G A C C C A		
<i>F</i>	G G T G A A C C A A T A A T A A A T T T C T A T G A C C C A		
<i>F.opt</i>	G G C G A G G C C C A T C A T C A A C T T C T A C G A C C C C G G T G A A C C A A T A A T A A A T T T C T A T G A C C C A		
	1450	1460	1470
<i>F.viral</i>	T T A G T A T T C C C C T C T G A T G A A T T T G A T G C A		
<i>F</i>	T T A G T A T T C C C C T C T G A T G A A T T T G A C G C G		
<i>F.opt</i>	C T G G T G T T C C C C T C C G A C G A A T T C G A C G C C T T A G T A T T C C C C T C T G A T G A A T T T G A C G C		
	1480	1490	1500
<i>F.viral</i>	T C A A T A T C T C A A G T C A A C G G A G A G A T T A A C		
<i>F</i>	T C A A T A T C T C A A G T C A A C G G A G A G A T T A A C		
<i>F.opt</i>	T C C A T T A G C C A A G T C A A C G G A G A G A T C A A C T C A A T A T C T C A A G T C A A C G G A G A G A T T A A C		
	1510	1520	1530
<i>F.viral</i>	C A G A G C C T A G C A T T T A T T C G T A A A T C C G A T		
<i>F</i>	C A G A G C T T A G C A T T T A T T C G T A A A T C C G A T		
<i>F.opt</i>	C A G A G C C T G G C C T T C A T C C G C A A G T C C G A C C A G A G C C T A G C A T T T A T T C G T A A A T C C G A T		
	1540	1550	1560
<i>F.viral</i>	G A A T T A T T A C A T A A T G T A A A T G C T G G T A A A		
<i>F</i>	G A A T T A T T A C A T A A T G T A A A T G C T G G G A A G		
<i>F.opt</i>	G A G C T G C T G C A C A A C G T C A A C G C T G G C A A G G A A T T A T T A C A T A A T G T A A A T G C T G T G G A A G		
	1570	1580	1590
<i>F.viral</i>	T C C A C C A C A A A T A T C A T G A T A A C T A C T A T A		
<i>F</i>	A G C A C C A C A A A T A T C A T G A T A A C T A C T A T A		
<i>F.opt</i>	A G C A C C A C C A A C A T C A T G A T C A C C A C C A T C A G C A C C A C A A A T A T C A T G A T A A C T A C T A T A		

Figure 2a(vi)

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11/40

	1600	1610	1620
<i>F.viral</i>	ATT T A T A G T G A T T A T A G T A A T A T T G T T A T C A		
<i>F</i>	ATT T A T A G T G A T T A T A G T A A T A T T G T T A T C A		
<i>F.opt</i>	AT C A T C G T G A T C A T C G T G A T C C T G C T G A G C		
	ATT T A T A G T G A T T A T A G T A A T A T T G T T A T C A		
	1630	1640	1650
<i>F.viral</i>	T T A A T T G C T G T T G G A C T G C T C T T A T A C T G T		
<i>F</i>	T T A A T T G C T G T T G G A C T G C T C T T A T A C T G T		
<i>F.opt</i>	C T G A T C G C C C G T G G G G C C T G C T G C T G T A C T G C		
	T T A A T T G C T G T T G G A C T G C T C T T A T A C T G T		
	1660	1670	1680
<i>F.viral</i>	A A G G C C A G A A G C A C A C C A G T C A C A C T A A G C		
<i>F</i>	A A G G C C A G A T C T A C A C C A G T C A C A C T A A G C		
<i>F.opt</i>	A A G G C C C G G A G C A C T C C C G T G A C C C T G A G C		
	A A G G C C A G A A G C A C A C C A G T C A C A C T A A G C		
	1690	1700	1710
<i>F.viral</i>	A A A G A T C A A C T G A G T G G T A T A A A T A A T A T T		
<i>F</i>	A A A G A T C A A C T G A G T G G T A T A A A T A A T A T T		
<i>F.opt</i>	A A G G A C C A G G C T G A G C G G C A T C A A C A A C A T C		
	A A A G A T C A A C T G A G T G G T A T A A A T A A T A T T		
	1720	1730	1740
<i>F.viral</i>	G C A T T T A G T A A C T A A		
<i>F</i>	G C A T T T A G T A A C T A A		
<i>F.opt</i>	G C C T T C A G C A A C T G A		
	G C A T T T A G T A A C T A A		

Figure 2a(vii)
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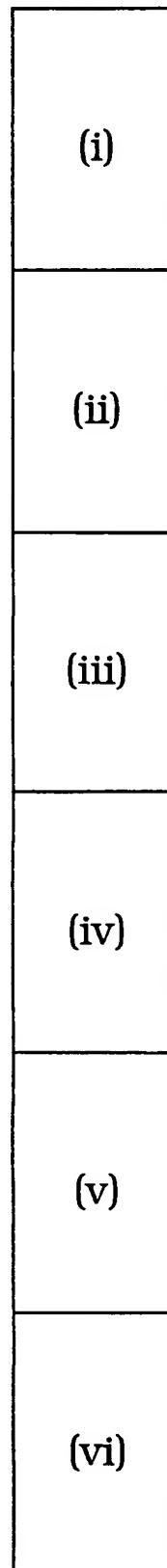


Figure 2b
SUBSTITUTE SHEET (RULE 26)

13/40

ClustalW Formatted Alignments

	10	20	30
<i>F.sol.viral</i>	ATGGAGTTGCTAATCCTCAAAGCAAAATGCA		
<i>F.sol</i>	ATGGAGTTGCTAATCCTCAAAGCAAAATGCA		
<i>F.sol.opt</i>	ATGGAGCTGCTGATCCTGAAGGCCAACGCC		
	ATGGAGTTGCTAATCCTCAAAGCAAAATGCA		
		40	
<i>F.sol.viral</i>	ATTACCCACAATCCTCACTGCAGTCACATT	50	60
<i>F.sol</i>	ATTACCCACAATCCTCACTGCAGTCACCTT		
<i>F.sol.opt</i>	ATCACCCACCATCCTGACCGCGGTGACCTT		
	ATTACCCACAATCCTCACTGCAGTCACCTT		
		70	
<i>F.sol.viral</i>	TGTTTTGCTTCTGGTCAAAACATCACTGAA	80	90
<i>F.sol</i>	TGTTTTGCTTCTGGTCAAAACATCACTGAA		
<i>F.sol.opt</i>	TGCTTCGCTCTGGCCAGAACATCACTGAG		
	TGTTTTGCTTCTGGTCAAAACATCACTGAA		
		100	
<i>F.sol.viral</i>	GAATTTTATCAATCAACATGCAGTGCA GTT	110	120
<i>F.sol</i>	GAATTTTATCAATCAACATGCAGTGCA GTT		
<i>F.sol.opt</i>	GAGTTCTACCCAGAGCACTTGTTCCGCTGTG		
	GAATTTTATCAATCAACATGCAGTGCA GTT		
		130	
<i>F.sol.viral</i>	AGCAAAAGGCTATCTTAGTGCTCTGAGAAC	140	150
<i>F.sol</i>	AGCAAAAGGATATCTTAGTGCTCTGAGAAC		
<i>F.sol.opt</i>	AGCAAGGGCTACCTGAGCGCCCTGAGGACC		
	AGCAAAAGGCTATCTTAGTGCTCTGAGAAC		
		160	
<i>F.sol.viral</i>	GGTTGGTATAACCAAGTGTATAACTATAGAA	170	180
<i>F.sol</i>	GGTTGGTATAACCAAGTGTATAACTATAGAA		
<i>F.sol.opt</i>	GGTTGGTACACCCAGCGTGTACACCATCGAG		
	GGTTGGTATAACCAAGTGTATAACTATAGAA		
		190	
<i>F.sol.viral</i>	TTAAGTAATATCAAGAAAAAATAAGTGTAAAT	200	210
<i>F.sol</i>	TTAAGTAATATCAAGAAAAAATAAGTGTAAAT		
<i>F.sol.opt</i>	CTGAGCAACATCAAGAACAAAGTGCAAC		
	TTAAGTAATATCAAGAAAAAATAAGTGTAAAT		
		220	
<i>F.sol.viral</i>	GGAACACAGATGCTAAGGTAAAATTGATAAAA	230	240
<i>F.sol</i>	GGTACCGATGCTAAGGTAAAATTGATAAAA		
<i>F.sol.opt</i>	GGCACCCGACGCCAAGGTGAAGCTGATCAAG		
	GGACCGATGCTAAGGTAAAATTGATAAAA		

Figure 2b(i)

SUBSTITUTE SHEET (RULE 26)

14/40

	250	260	270
<i>F.sol.viral</i>	CAAGAATTAGATAAAATATAAAAATGCTGTA		
<i>F.sol</i>	CAAGAATTAGATAAAATATAAAAATGCTGTA		
<i>F.sol.opt</i>	CAAGAGCTGGACAAAGTACAAGAACGCCGTG CAAGAATTAGATAAAATATAAAAATGCTGTA		
	280	290	300
<i>F.sol.viral</i>	ACAGAATTGCAGTTGCTCATGCAAAGCACAA		
<i>F.sol</i>	ACAGAATTGCAGTTGCTCATGCAGTCGACAA		
<i>F.sol.opt</i>	ACCGAGCTGCAACTGCTGATGCAAGTCGACT ACAGAATTGCAGTTGCTCATGCAGTCGACAA		
	310	320	330
<i>F.sol.viral</i>	CAAGCAACAAACAATCGAGCCAGAAGAGAA		
<i>F.sol</i>	CAAGCAACAAACAATCGAGCCAGAAGAGAA		
<i>F.sol.opt</i>	CAAGCCACCAACAACAGAGGCCGAGAGAG CAAGCAACAAACAATCGAGCCAGAAGAGAA		
	340	350	360
<i>F.sol.viral</i>	CTACCAAGGTTTATGAATTATAACACTCAAC		
<i>F.sol</i>	CTACCTAGGTTTATGAATTATAACACTCAAC		
<i>F.sol.opt</i>	CTGCCCGCTTCAATGAACTACACCCCTGAAC CTACC AGGTTTATGAATTATAACACTCAAC		
	370	380	390
<i>F.sol.viral</i>	AATGCCAAAAACCAATGTAACATTAAGC		
<i>F.sol</i>	AATGCCAAAAACCAATGTAACACACTTTTCG		
<i>F.sol.opt</i>	AACGCCAAGGAAGACCAACGTTGACCCCTGTCC AATGCCAAAAACCAATGTAACACT TCC		
	400	410	420
<i>F.sol.viral</i>	AAGAAAAGGAAAAGAAGATTCTTGGTTTT		
<i>F.sol</i>	AAGAAAAGGAAAAGAAGATTCTTGGTTTT		
<i>F.sol.opt</i>	AAGAAAGAGGAAGCGCCGCTTCCCTGGGCTTC AAGAAAAGGAAAAGAAGATTCTTGGTTTT		
	430	440	450
<i>F.sol.viral</i>	TTGTAGGTGTTGGATCTTGCAATCGCCAGT		
<i>F.sol</i>	TTGTAGGTGTTGGATCCGCAATCGCCAGT		
<i>F.sol.opt</i>	CTGCTGGCGTGGCTCCGCCATTGCCAGT TTGTAGGTGTTGGATCCGCAATCGCCAGT		
	460	470	480
<i>F.sol.viral</i>	GGCGTTGCTGTATCTAACGGTCCCTGCACCTA		
<i>F.sol</i>	GGCGTTGCTGTATCTAACGGTCCCTGCATCTA		
<i>F.sol.opt</i>	GGCGTGGCGTGGCTCCAAAGGTGCTGCACCTG GGCGTTGCTGTATCTAACGGTCCCTGCACCTA		
	490	500	510
<i>F.sol.viral</i>	GAAGGGGAAGTGAACAAAGATCAAAGTGC		
<i>F.sol</i>	GAAGGGGAAGTGAACAAAGATCAAAGTGC		
<i>F.sol.opt</i>	GAGGGCGAGGTGAACAAAGATCAAAGAGTGC GAGGGGGAAAGTGAACAAAGATCAAAGTGC		

Figure 2b(ii)
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	520	530	540
<i>F.sol.viral</i>	CT A C T A T C C A C A A A C A A G G C T G T A G T C A G C		
<i>F.sol</i>	CT A C T A T C C A C A A A C A A G G C T G T A G T C A G C		
<i>F.sol.opt</i>	CT G C T G T C C A C T A A C A A G G C C G T G G T G A G C		
	CT A C T A T C C A C A A A C A A G G C T G T A G T C A G C		
	550	560	570
<i>F.sol.viral</i>	T T A T C A A A T G G A G T T A G T G T C T T A A C C A G C		
<i>F.sol</i>	T T A T C A A A T G G A G T T A G T G T C T T A A C C A G C		
<i>F.sol.opt</i>	CT G A G C A A C G G C G T G A G T G T G C T G A C T A G C		
	TT A T C A A A T G G A G T T A G T G T C T T A A C C A G C		
	580	590	600
<i>F.sol.viral</i>	A A A G T G T T A G A C C T C A A A A A C T A T A T A G A T		
<i>F.sol</i>	A A A G T G T T A G A C C T C A A A A A C T A T A T A G A T		
<i>F.sol.opt</i>	A A G G T G C T G G A C C T G A A G A A C T A C A T C G A C		
	A A A G T G T T A G A C C T C A A A A A C T A T A T A G A T		
	610	620	630
<i>F.sol.viral</i>	A A A C A A T T G T T A C C T A T T G T G A A C A A G C A A		
<i>F.sol</i>	A A A C A A T T G T T A C C T A T T G T g A a c a a g c a a		
<i>F.sol.opt</i>	A A G C A A T T G C T G C C C A T C G T G A A C A A G C A G		
	A A A C A A T T G T T A C C T A T T G T g a a c a a g c a a		
	640	650	660
<i>F.sol.viral</i>	A G C T G C A G C A T A T C A A A T A T A G A A A C T G T G		
<i>F.sol</i>	A G C T G C A G C A T A T C A A A T A T A G A A A C T G T G		
<i>F.sol.opt</i>	T C C T G T A G C A T C T C C A A C A T C G A G A C T G T G		
	A G C T G C A G C A T A T C A A A T A T A G A A A C T G T G		
	670	680	690
<i>F.sol.viral</i>	A T A G A G T T C C A A C A A A A G A A C A A C A G A C T A		
<i>F.sol</i>	A T A G A G T T C C A A C A A A A G A A C A A C A G A C T A		
<i>F.sol.opt</i>	A T C G A G T T C C A G G C A G A A G A A C A A C C G C C T G		
	A T A G A G T T C C A A C A A A A G A A C A A C A G A C T A		
	700	710	720
<i>F.sol.viral</i>	C T A G A G A T T A C C A G G G A A T T T A G T G T T A A T		
<i>F.sol</i>	C T A G A G A T T A C C A G G G A A T T T A G T G T T A A T		
<i>F.sol.opt</i>	C T G G A A A T C A C C C G G G A G T T C A G T G T g a a c		
	C T A G A G A T T A C C A G G G A A T T T A G T G T T A A T		
	730	740	750
<i>F.sol.viral</i>	G C A G G T G T A A C T A C A C C T G T A A G G C A C T T A C		
<i>F.sol</i>	G C A G G T G T A A C T A C A C C T G T A A G G C A C T T A C		
<i>F.sol.opt</i>	G C T G G C G T G A C C A C T C C T G T C T C C A C C T A C		
	G C A G G T G T A A C T A C A C C T G T A A G G C A C T T A C		
	760	770	780
<i>F.sol.viral</i>	A T G T T A A C T A A T A G T G A A T T A T T G T C A T T A		
<i>F.sol</i>	A T G T T A A C T A A T A G T G A A T T A T T G T C A T T A		
<i>F.sol.opt</i>	A T G C T G A C C A A C A G G C G A G C T G C T G A G G C C T G		
	A T G T T A A C T A A T A G T G A A T T A T T G T C A T T A		

Figure 2b(iii)

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	790	800	810
<i>F.sol.viral</i>	AT C A A T G A T A T G C C T A T A A C A A A T G A T C A G		
<i>F.sol</i>	AT C A A T G A T A T G C C T A T A A C A A A T G A T C A G		
<i>F.sol.opt</i>	AT C A A C G A C A T G C C C A T C A C C A A C G A C C A G		
	AT C A A T G A T A T G C C T A T A A C A A A T G A T C A G		
	820	830	840
<i>F.sol.viral</i>	A A A A A G T T A A T G T C C A A C A A T G T T C A A A T A		
<i>F.sol</i>	A A A A A G T T A A T G T C C A A C A A T G T T C A A A T A		
<i>F.sol.opt</i>	A A G A A G C T T A T G T C C A A C A A C G T G C A G A T C		
	A A A A A G T T A A T G T C C A A C A A T G T T C A A A T A		
	850	860	870
<i>F.sol.viral</i>	G T T A G A C A G C A A A G T T A C T C T A T C A T G T C C		
<i>F.sol</i>	G T T A G A C A G C A A A G T T A C T C T A T C A T G T C C		
<i>F.sol.opt</i>	G T G A G G C A G C A G G C T A C T C C A T C A T G A G C		
	G T T A G A C A G C A A A G T T A C T C T A T C A T G T C C		
	880	890	900
<i>F.sol.viral</i>	A T A A T A A A A G A G G G A A G T C T T A G C A T A T G T A		
<i>F.sol</i>	A T A A T A A A A G A G G G A A G T C T T A G C A T A T G T A		
<i>F.sol.opt</i>	A T C A T C A A G G G A G G G A G T G C T G G C C T A T G T G		
	A T A A T A A A A G A G G G A A G T C T T A G C A T A T G T A		
	910	920	930
<i>F.sol.viral</i>	G T A C A A T T A C C A C T A T A T G G T G T T A T A G A T		
<i>F.sol</i>	G T A C A A T T A C C A C T A T A T G G T G T T A T A G A T		
<i>F.sol.opt</i>	G T G C A G C T G C C C C T G T A C G G C G T C A T C G A T		
	G T A C A A T T A C C A C T A T A T G G T G T T A T A G A T		
	940	950	960
<i>F.sol.viral</i>	A C A C C C T G T T G G A A A C T A C A C A C A T C C C C T		
<i>F.sol</i>	A C A C C C T G T T G G A A A C T A C A C A C A T C C C C T		
<i>F.sol.opt</i>	A C C C C T T G C T G G A A G C T G C A C A C C A G C C C C		
	A C A C C C T G T T G G A A A C T A C A C A C A T C C C C T		
	970	980	990
<i>F.sol.viral</i>	C T A T G T A C A A C C A A C A C A A A A A G A A G G G T C C		
<i>F.sol</i>	C T A T G T A C A A C C A A C A C A C A A A A G A A G G G T C C		
<i>F.sol.opt</i>	C T G T G C A C C A C C A A C A C A C C A A G G A G G G C A G C		
	C T A T G T A C A A C C A A C A C A A A A G A A G G G T C C		
	1000	1010	1020
<i>F.sol.viral</i>	A A C A T C T G T T T A A C A A G A A C T G A C A G A G G A		
<i>F.sol</i>	A A C A T C T G T T T A A C A A G A A C T G A C A G A G G A		
<i>F.sol.opt</i>	A A C A T C T G C C T G A C C C G G A C C G A C C G C G G C		
	A A C A T C T G T T T A A C A A G A A C T G A C A G A G G A		
	1030	1040	1050
<i>F.sol.viral</i>	T G G T A C T G T G A C A A T G C A G G A T C A G T A T C T		
<i>F.sol</i>	T G G T A C T G T G A C A A T G C A G G A T C A G T A T C T		
<i>F.sol.opt</i>	T G G T A C T G T G A C A A C G C T G G C T C G G T G A G C		
	T G G T A C T G T G A C A A T G C A G G A T C A G T A T C T		

Figure 2b(iv)
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	1060	1070	1080
<i>F.sol.viral</i>	TTCTTCCCACAAGCTGAAACATGTAAAGTT		
<i>F.sol</i>	TTCTTCCCACAAGCTGAAACATGTAAAGTT		
<i>F.sol.opt</i>	TTCTTCCCCTCAAGCTGAAACACTGCAAGGTC	TTCTTCCCACAAGCTGAAACATGTAAAGTT	
	1090	1100	1110
<i>F.sol.viral</i>	CAATCAAAATCGAGTATTGGTGACACAAATG		
<i>F.sol</i>	CAATCAAAATCGAGTATTGGTGACACAAATG		
<i>F.sol.opt</i>	CAGAGCAACAGAGTGTCTGTGACACCATG	CAATCAAAATCGAGTATTGGTGACACAAATG	
	1120	1130	1140
<i>F.sol.viral</i>	AACAGTTAACATTACCAAGTGAAGTAAAT		
<i>F.sol</i>	AACAGTTAACATTACCAAGTGAAGTAAAT		
<i>F.sol.opt</i>	AACTCCCTGACCCCTGCCCTCCGAGGTGAAAC	AACAGTTAACATTACCAAGTGAAGTAAAT	
	1150	1160	1170
<i>F.sol.viral</i>	CTCTGCAATGTTGACATATTCAACCCCCAAA		
<i>F.sol</i>	CTCTGCAATGTTGACATATTCAACCCCCAAA		
<i>F.sol.opt</i>	CTGTGCAACCGTGGATATCTTCAACCCCCAAG	CTCTGCAATGTTGACATATTCAACCCCCAAA	
	1180	1190	1200
<i>F.sol.viral</i>	TATGATTGTAaaaATTATGACTTCACAAACAA		
<i>F.sol</i>	TATGATTGTAaaaATTATGACTTCACAAACAA		
<i>F.sol.opt</i>	TATGACTGCAAGATCATGACCTCCAAGGACC	TATGATTGTAaaaATTATGACTTCACAAACAA	
	1210	1220	1230
<i>F.sol.viral</i>	GATGTAAGCAGCTCCGTTATCACATCTCTA		
<i>F.sol</i>	GATGTAAGCAGCTCCGTTATCACATCTCTA		
<i>F.sol.opt</i>	GATGTCCTCGAGCTCCGTTGATCACCCAGCCTG	GATGTAAGCAGCTCCGTTATCACATCTCTA	
	1240	1250	1260
<i>F.sol.viral</i>	GGAGCCATTGTGTCATGCTATGGCAAAACT		
<i>F.sol</i>	GGAGCCATTGTGTCATGCTATGGCAAAACT		
<i>F.sol.opt</i>	GGCGCCATTGTGTCCTGCTATGGCAAGACC	GGAGCCATTGTGTCATGCTATGGCAAAACT	
	1270	1280	1290
<i>F.sol.viral</i>	AAATGTACAGCATCCAAATAAAAAATCGTGGAA		
<i>F.sol</i>	AAATGTACAGCATCCAAATAAAAAATCGTGGAA		
<i>F.sol.opt</i>	AAAGTGCACCGGCCAGCAACAAAGAACCGGGGGC	AAATGTACAGCATCCAAATAAAAAATCGTGGAA	
	1300	1310	1320
<i>F.sol.viral</i>	ATCATAAAAGACATTTCTAACGGGTGCGAT		
<i>F.sol</i>	ATCATAAAAGACATTTCTAACGGGTGCGAT		
<i>F.sol.opt</i>	ATCATAAAAGACCTTCAGCAATGGGTGCGAC	ATCATAAAAGACATTTCTAACGGGTGCGAT	

Figure 2b(v)

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	1330	1340	1350
<i>F.sol.viral</i>	TATGTATCAAATAAAGGGGTGGACACTGTG		
<i>F.sol</i>	TATGTATCAAATAAAGGGGTGGACACTGTG		
<i>F.sol.opt</i>	TACGTTTCAAAACAGGGCGTGGACACTGTG TATGTATCAAATAAAGGGGTGGACACTGTG		
	1360	1370	1380
<i>F.sol.viral</i>	TCTGTAGGTAAACACATTATATTATGTAAAT		
<i>F.sol</i>	TCTGTAGGTAAACACATTATATTATGTAAAT		
<i>F.sol.opt</i>	TCCGTGGGCAACACCCTGTACTACGTGAAC TCTGTAGGTAAACACATTATATTATGTAAAT		
	1390	1400	1410
<i>F.sol.viral</i>	AAGCAAGAAGGTAAAAGTCTCTATGTAAAA		
<i>F.sol</i>	AAGCAAGAAGGTAAAAGTCTCTATGTAAAA		
<i>F.sol.opt</i>	AAGCAAGAAGGGCAAGAGCCTGTATGTGAAG AAGCAAGAAGGTAAAAGTCTCTATGTAAAA		
	1420	1430	1440
<i>F.sol.viral</i>	GGTGAACCAATAATAAAATTCTATGACCCA		
<i>F.sol</i>	GGTGAACCAATAATAAAATTCTATGACCCA		
<i>F.sol.opt</i>	GGCGAGCCCATCATCAAACCTTCTACGACCCC GGTGAACCAATAATAAAATTCTATGACCCA		
	1450	1460	1470
<i>F.sol.viral</i>	TTAGTATTCCCCCTCTGATGAATTTGATGCA		
<i>F.sol</i>	TTAGTATTCCCCCTCTGATGAATTTGACGCC		
<i>F.sol.opt</i>	CTGGTGTCCCCCTCCGACGAATTCTGACGCC TTAGTATTCCCCCTCTGATGAATTTGACGC		
	1480	1490	1500
<i>F.sol.viral</i>	TCAATATCTCAAGTCAACCGAGAAGATTAAC		
<i>F.sol</i>	TCAATATCTCAAGTCAACCGAGAAGATTAAC		
<i>F.sol.opt</i>	TCCATTAGCCAAGTCAACCGAGAAGATCAAC TCAATATCTCAAGTCAACCGAGAAGATTAAC		
	1510	1520	1530
<i>F.sol.viral</i>	CAGAGCCTAGCATTATTCTGTAATCCGAT		
<i>F.sol</i>	CAGAGCTTAGCATTATTCTGTAATCCGAT		
<i>F.sol.opt</i>	CAGAGCCTGGCTTCCATCCGCAAGTCCGAC CAGAGCCTAGCATTATTCTGTAATCCGAT		
	1540	1550	1560
<i>F.sol.viral</i>	GAATTATTACATAATGTAAATGCTGGTAAA		
<i>F.sol</i>	GAATTATTACATAATGTAAATGCTGGGAAAG		
<i>F.sol.opt</i>	GAGCTGCTGCACAACGTCAACCGCTGGCAAG GAATTATTACATAATGTAAATGCTGG AAG		
	1570	1580	1590
<i>F.sol.viral</i>	TCCACCCACAAATTAA		
<i>F.sol</i>	AGCACCCACAAATTAA		
<i>F.sol.opt</i>	AGCACCCACCAACTGA AGCACCCACAAATTAA		

Figure 2b(vi)

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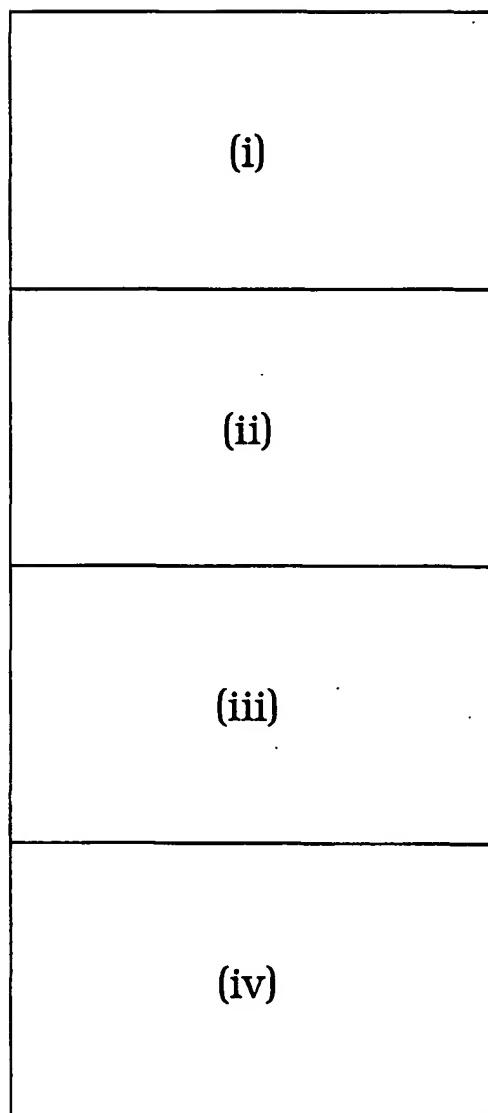


Figure 3a
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Sequence of the *Pst*I to *Bam*H1 fragment as found in the plasmid PCICO.F.F1.opt (see Fig 4b)

Figure 3a(i)

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510 520 530 540 550 560 570 580 590 600
 CTGGAGGGCG AGGTGAACAA GATCAAGAGT GCCCCTGCTGT CCACTAACAA GGCCGGGGTG AGCCTGAGCA ACGGCCGTGAG TGTCGTGACT AGCAAGGGTGC
 GACCTCCGC TCCACTTGTCTCA CGGGACGACA GGTGATTGTT CCGGCCACCAC TCGGACTCGT TGCCGGACTCT ACACGACTGA TCGTGTCACAG
 L E G E V N K I K S A L L S T N K A V V S L S N G V S V L T S K V>
 _____ a >

>MfeI
 610 620 630 640 650 660 670 680 690 700
 TGGACCTGAA GAACTACATC GACAAGCAAT TGCTGCCAT CGTGAAACAAG CAGTCCCTGTA GCATCTCCAA CATCGAGACT GTGATCGAGT TCAGCCAGAA
 ACCTGACTT CTTGATGTTA CGTGTCTGTTA ACGACGGGTA GCACTTGTTC GTCAGGACAT CGTAGAGGTT GTAGCTCTGA CACTAGCTCA AGGTGCGTCT
 L D L K N Y I D K Q L L P I V N K Q S C S I S N I E T V I E F Q Q K>
 _____ a >

>SmaI
 710 720 730 740 750 760 770 780 790 800
 GAAACACCGC CTGGCTGGAAA TCACCCGGGA GTTCAGTGGTG AACGGCTGGCG TGACCACTTC TGTCCTCCACC TACATGCTGA CCAACAGCGA GCTGCTGAGC
 CCTGCTGGCG GACGACCTT AGTGGCCCT CAAGTCACAC TTGGCACCGC ACTGGTGAGG ACAGAGGTT ATGTTACGACT GGTGTCGCT CGACGACTCG
 N N R L L E I T R E F S V N A G V T T P V S T Y M L T N S E L L S>
 _____ a >

>HindIII
 810 820 830 840 850 860 870 880 890 900
 CTGATCAAG ACATGCCAT CACCAACGAC CAGAAGAACG TTATGCTCAA CAACGAGGC ATCGTGAGCG AGCATCATCA CTCCATCATG AGCATCATCA
 GACTAGTTGC TTGACGGGTA GTGGTGTGCTG GTCTCTTCG AATAACAGGT GTGCACTCG TAGCACTCCG TCGTCTCGAT GAGGTAGTAC TCGTAGTGT
 L I N D M P I T N D Q K K L M S N N V Q I V R Q Q S Y S I M S I I>
 _____ a >

>ClaI
 910 920 930 940 950 960 970 980 990 1000
 AGGGAGGT GCTGGCCCTAT GTGGTGCAGC TGCCCTGTA CGGGTCACTC GATACCCTT GCTGGAGGT GCACACCGC CCCCTGTGCA CCACCAACAC
 TCCTCTCCA CGACCGGATA CACCAAGTCG ACGGGGACAT GCGCGCTAG CTATGGGAA CGACCTTCGA CGTGTGGTGC GGGGACACGT GGGGTTGTG
 K E E V L A Y V V Q L P L Y G V I D T P C W K L H T S P L C T T N T>
 _____ a >

Figure 3a(ii)

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Figure 3a(iii)

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Figure 3a(iv)

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Figure 3b

Sequence of the PstI to BamHI fragment as found in the plasmid pCICO-F-opt (see fig 4b)

```

>PstI
|   | 10    20    30    40    50    60    70    80    90    100
|   | CGTCAGTCAC CGTCTTGAC ACCATGGAC TGCTGATCCT GAAGGCCAAC GCCATCACCA CCGGGTGACC TTCTGCCTCG CCTCTGGCCA
GACGTCACTG GCAGGAACCTG TGGTACCTCG ACGACTAGGA CTTCCGGTGT CGTAGTGGT GGTAGGACTG GCGCCACTGG AAGACGAAGC GGAGACGGT
M E L L I L K A N A I T T I L T A V T F C F A S G Q>
a _____ a >

>BstEII
|   | 110   120   130   140   150   160   170   180   190   200
|   | GAAACATCACT GAGGAGTTCT ACCAGAGCAC AACGGCACCG ACGCCAAAGGT GAAGGTGATC AAGCAAGGC TGAGACAAGTA CAAGAACGCC GTGACCGAGC
CTTGTAGTGA CTCCCTCAAGA TGGTCTCGTG AACAAAGGCGA CACTCGTTCC CGATGGACTC GCGGGACTCC TGGCCAAACCA TGTGGTCCGA CTAGGGTAG
N I T E F Y Q S T C S A V S K G Y L S A L R T G W Y T S V I T I>
a _____ a >

>AgeI
|   | 210   220   230   240   250   260   270   280   290   300
|   | GAGCTGAGCA ACATCAAGAA GAAACAAGTGC AACGGCACCG ACGCCAAAGGT GAAGGTGATC AAGCAAGGC TGAGACAAGTA CAAGAACGCC GTGACCGAGC
CTCGACTCGT TGTAGTTCTT CTGGTTCACT TTGCGTGGC TGCGGTTCACT CTTCGACTAG TTCGTTCTCG ACCTGTTCAT GTTCTGGG CACTGGCTCG
E L S N I K K N K C N G T D A K V K L I K Q E L D K Y K N A V T E>
a _____ a >

>BstXI
|   | 310   320   330   340   350   360   370   380   390   400
|   | TGGAACTGCT GATGGAGTCG ACTCAAAGCA CCAACAAACAG AGCCCCGAGA GAGCTGGCCC GCTTCATGAA CTACACCTG ACAACAGCCA AGAAAGACCAA
ACGTTGAGCA CTAGCTCGC TGAAGTTCGGT GGTTGGTGTCT CTCGACGGGTCT CGAAGTACTT GATGTGGAC TGTGGGT TCTTCTGGTT
L Q L M Q S T Q A T N N A R R E L P R F M N Y T L N N A K K T N>
a _____ a >

>BstXI
|   | 410   420   430   440   450   460   470   480   490   500
|   | CGTGACCCCTG TCCAAGAAGA GGAAGCGCGC CTTCTGGC TTCCTGGC CGCTGGCTC CGCCATTGCC AGTGGCGTGG CGGTGTCCAA GGTGGTGCAC
GCACGGGAC AGGTCTTCT CTTCTGGCGC GAAGGACCCG AAGGACGCC CGCACTGGGAC TCAACGGCACC GGCACAGGGT CCACGACGCTG
V T L S K K R K R F L G F L L G V G S A I A S G V A V S K V L H>
a _____ a >

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Figure 3b(i)

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Figure 3b(ii)

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Figure 3b(iv)

Assembly of F synthetic DNA fragments

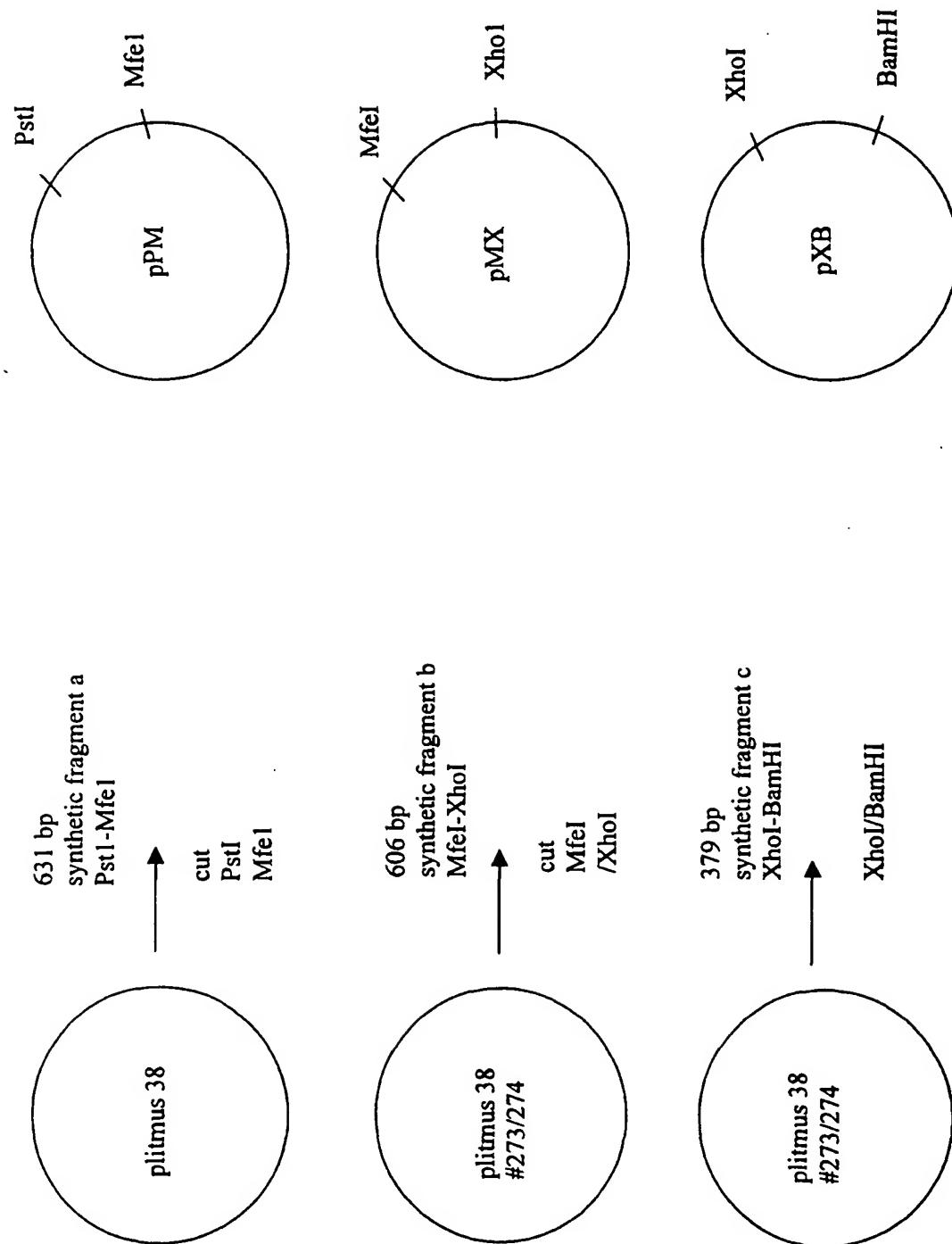


Figure 4a

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Assembly of F in pCICO expression vector

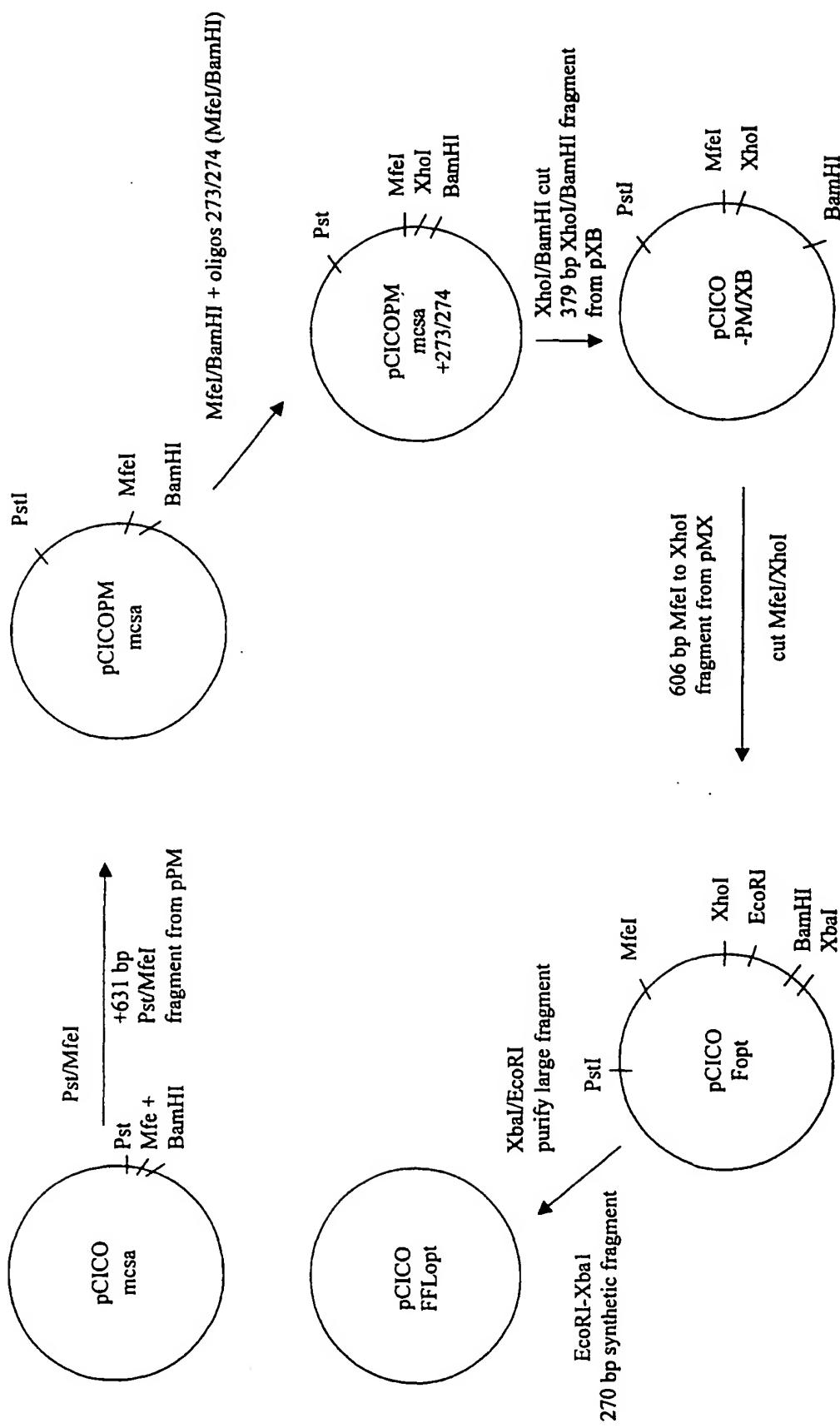


Figure 4b

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**Autoradiograph of immunoprecipitation of
35-S labelled transfected cell supernatants**

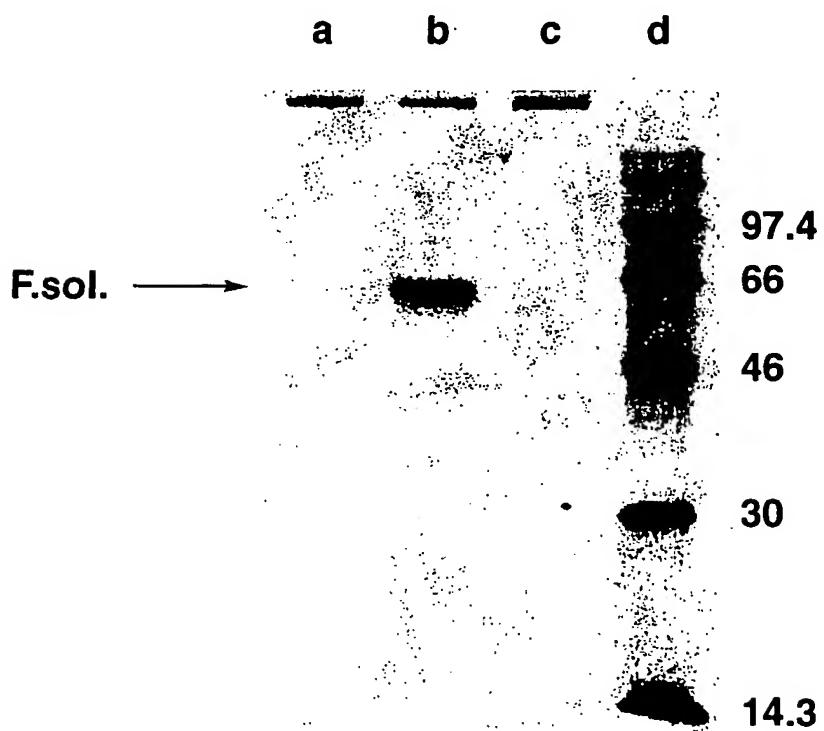


Figure 5

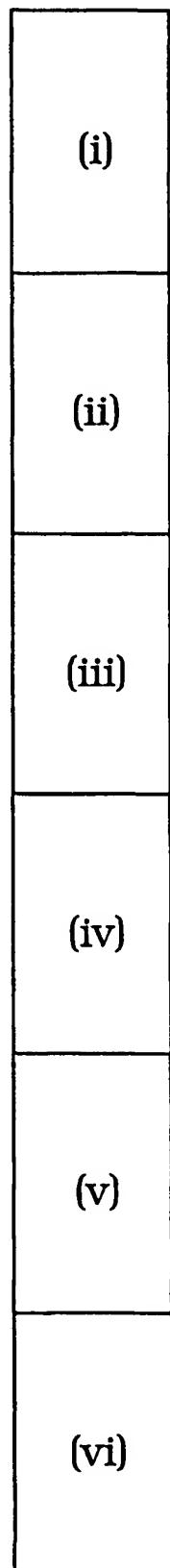


Figure 6
SUBSTITUTE SHEET (RULE 26)

ClustalW Formatted Alignments

	10	20	30
F.viral	ATGGAGTTGCTAATCCTCAAAGCAAAATGCA		
F.nat	ATGGAGTTGCTAATCCTCAAAGCAAAATGCA		
	ATGGAGTTGCTAATCCTCAAAGCAAAATGCA		
		40	50
F.viral	ATTACCAACAATCCTCACTGCAGTCACATT		
F.nat	ATTACCAACAATGCTCACTGCAGTCACATT		
	ATTACCAACAATCCTCACTGCAGTCACATT		
		60	
		70	80
F.viral	TGTTTGTCTTCTGGTCAAACATCACTGAA		
F.nat	TGTTTGTCTTCTGGTCAAACATCACTGAA		
	TGTTTGTCTTCTGGTCAAACATCACTGAA		
		90	
		100	110
F.viral	GAATTTATCAATCAACATGCAGTGCAAGTT		
F.nat	GAATTTATCAATCAACATGCAGTGCAAGTT		
	GAATTTATCAATCAACATGCAGTGCAAGTT		
		120	
		130	140
F.viral	AGCAAAGGCTATCTTAGTGCTCTGAGAACT		
F.nat	AGCAAAGGCTATCTTAGTGCTCTGAGAACT		
	AGCAAAGGCTATCTTAGTGCTCTGAGAACT		
		150	
		160	170
F.viral	GGTTGGTATACCAAGTGTATAACTATAGAA		
F.nat	GGTTGGTATACCAAGTGTATAACCATAAGAA		
	GGTTGGTATACCAAGTGTATAAACATAAGAA		
		180	
		190	200
F.viral	TTAAGTAATATCAAGAAAAATAAGTGTAAAT		
F.nat	CTAAGTAATATCAAGAAAAATAAGTGTAAAT		
	TAAGTAATATCAAGAAAAATAAGTGTAAAT		
		210	
		220	230
F.viral	GGAACAGATGCTAAGGTAAAATTGATAAAA		
F.nat	GGAACAGATGCCAAGGTAAAATTGATAAAA		
	GGAACAGATGC AAGGTAAAATTGATAAAA		
		240	
		250	260
F.viral	CAAGAATTAGATAAAATATAAAAAATGCTGTA		
F.nat	CAAGAATTAGATAAAATATAAAAAATGCTGTA		
	CAAGAATTAGATAAAATATAAAAAATGCTGTA		
		270	
		280	290
F.viral	ACAGAATTGCAGTTGCTCATGCAAGCACA		
F.nat	ACAGAATTGCAGTTGCTCATGCAAGCACA		
	ACAGAATTGCAGTTGCTCATGCAAGCACA		
		300	

Figure 6(i)
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	310	320	330
<i>F.viral</i>	CAAGCAACAAACAATCGAGCCAGAAGAGAA		
<i>F.nat</i>	CAAGCAACAAACAATCGAGCCAGAAGAGAA		
	CAAGCAACAAACAATCGAGCCAGAAGAGAA		
	340	350	360
<i>F.viral</i>	CTACCAAGGTTATGAATTATAACACTCAAC		
<i>F.nat</i>	CTACCAAGGTTATGAATTATAACACTCAAC		
	CTACCAAGGTTATGAATTATAACACTCAAC		
	370	380	390
<i>F.viral</i>	AATGCCAAAAAACCAATGTAAACATTAAGC		
<i>F.nat</i>	AATGCCAAAAAACCAATGTAAACATTAAGC		
	AATGCCAAAAAACCAATGTAAACATTAAGC		
	400	410	420
<i>F.viral</i>	AAGAAAAGGAAAAGAAGATTTCCTGGTTTT		
<i>F.nat</i>	AAGAAAAGGAAAAGAAGATTTCCTGGTTTT		
	AAGAAAAGGAAAAGAAGATTTCCTGGTTTT		
	430	440	450
<i>F.viral</i>	TTGTTAGGTGTTGGATCTGCAATCGCCAGT		
<i>F.nat</i>	TTGTTAGGTGTTGGATCTGCAATCGCCAGT		
	TTGTTAGGTGTTGGATCTGCAATCGCCAGT		
	460	470	480
<i>F.viral</i>	GGCGTTGCTGTATCTAAGGTCCCTGCACCTA		
<i>F.nat</i>	GGCGTTGCTGTATCTAAGGTCCCTGCACCTA		
	GGCGTTGCTGTATCTAAGGTCCCTGCACCTA		
	490	500	510
<i>F.viral</i>	GAAGGGGAAGTGAACAAAGATCAAAAGTGCT		
<i>F.nat</i>	GAAGGGGAAGTGAACAAAGATCAAAAGTGCT		
	GAAGGGGAAGTGAACAAAGATCAAAAGTGCT		
	520	530	540
<i>F.viral</i>	CTACTATCCACAAACAAAGGCTGTAGTCAGC		
<i>F.nat</i>	CTACTATCCACAAACAAAGGCTGTAGTCAGC		
	CTACTATCCACAAACAAAGGCTGTAGTCAGC		
	550	560	570
<i>F.viral</i>	TTATCAAATGGAGTTAGTGTCTTAACCAGC		
<i>F.nat</i>	TTATCAAATGGAGTTAGTGTCTTAACCAGC		
	TTATCAAATGGAGTTAGTGTCTTAACCAGC		
	580	590	600
<i>F.viral</i>	AAAGTGTAGACCTCAAAACTATATAAGAT		
<i>F.nat</i>	AAAGTGTAGACCTCAAAACTATATAAGAT		
	AAAGTGTAGACCTCAAAACTATATAAGAT		
	610	620	630
<i>F.viral</i>	AAACAAATTGTTACCTATTGTGAACAAGCAA		
<i>F.nat</i>	AAACAAATTGTTACCTATTGTGAACAAGCAA		
	AAACAAATTGTTACCTATTGTGAACAAGCAA		

Figure 6(ii)

SUBSTITUTE SHEET (RULE 26)

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	640	650	660
<i>F.viral</i>	AGCTGCAGCATATCAAA	TATAGAAACTGTG	
<i>F.nat</i>	AGCTGCAGCATATCAAA	TATAGAAACTGTG	
	AGCTGCAGCATATCAAA	TATAGAAACTGTG	
	670	680	690
<i>F.viral</i>	ATAGAGTTCCAAACAAA	AGAACACAGACTA	
<i>F.nat</i>	ATAGAGTTCCAAACAAA	AGAACACAGACTA	
	ATAGAGTTCCAAACAAA	AGAACACAGACTA	
	700	710	720
<i>F.viral</i>	CTAGAGATTACCAAGGG	AATTAGTGTAAAT	
<i>F.nat</i>	CTAGAGATTACCAAGGG	AATTAGTGTAAAT	
	CTAGAGATTACCAAGGG	AATTAGTGTAAAT	
	730	740	750
<i>F.viral</i>	GCAGGGTGTAACTACAC	CCTGTAAAGCACTTAC	
<i>F.nat</i>	GCAGGGTGTAACTACAC	CCTGTAAAGCACTTAC	
	GCAGGGTGTAACTACAC	CCTGTAAAGCACTTAC	
	760	770	780
<i>F.viral</i>	ATGTTAACTTAATAGTGA	ATTATTGTCAATT	
<i>F.nat</i>	ATGTTAACTTAATAGTGA	ATTATTGTCAATT	
	ATGTTAACTTAATAGTGA	ATTATTGTCAATT	
	790	800	810
<i>F.viral</i>	ATCAATGATAATGCC	CTATAAACAAA	TGATCAG
<i>F.nat</i>	ATCAATGATAATGCC	CTATAAACAAA	TGATCAG
	ATCAATGATAATGCC	CTATAAACAAA	TGATCAG
	820	830	840
<i>F.viral</i>	AAAAAGTTAATGTC	CCAACAAATGTT	CAAATA
<i>F.nat</i>	AAAAAGTTAATGTC	CCAACAAATGTT	CAAATA
	AAAAAGTTAATGTC	CCAACAAATGTT	CAAATA
	850	860	870
<i>F.viral</i>	GTTAGACAGCAAAGT	TACTCTATCATGTCC	
<i>F.nat</i>	GTTAGACAGCAAAGT	TACTCTATCATGTCC	
	GTTAGACAGCAAAGT	TACTCTATCATGTCC	
	880	890	900
<i>F.viral</i>	ATAATAAAAGAGGAAAG	TCTTAGCATATGTA	
<i>F.nat</i>	ATAATAAAAGAGGAAAG	TCTTAGCATATGTA	
	ATAATAAAAGAGGAAAG	TCTTAGCATATGTA	
	910	920	930
<i>F.viral</i>	GTACAATTACCACTAT	ATGGTGTATAGAT	
<i>F.nat</i>	GTACAATTACCACTAT	ATGGTGTATAGAT	
	GTACAATTACCACTAT	ATGGTGTATAGAT	
	940	950	960
<i>F.viral</i>	ACACCCCTGTTGGAAAC	TACACACACATCCCC	
<i>F.nat</i>	ACACCCCTGTTGGAAAC	TACACACACATCCCC	
	ACACCCCTGTTGGAAAC	TACACACACATCCCC	

Figure 6(iii)

SUBSTITUTE SHEET (RULE 26)

	970	980	990
<i>F.viral</i>	CTATGTACAACCAACACACA	AAAAGAAGGGTCC	
<i>F.nat</i>	CTATGTACAACCAACACACA	AAAAGAAGGGTCC	
	1000	1010	1020
<i>F.viral</i>	AACATCTGTTAACAAAGAACTGACAGAGGA		
<i>F.nat</i>	AACATCTGTTAACAAAGAACTGACAGAGGA		
	1030	1040	1050
<i>F.viral</i>	TGGTACTG TGACAATGCAGGATCAGTATCT		
<i>F.nat</i>	TGGTACTG TGACAATGCAGGATCAGTATCT		
	1060	1070	1080
<i>F.viral</i>	TTCTTCCCACAAGCTGAAACATG TAAAGTT		
<i>F.nat</i>	TTCTTCCCACAAGCTGAAACATG TAAAGTT		
	1090	1100	1110
<i>F.viral</i>	CAATCAAATCGAGTATT TTGTGACACAAATG		
<i>F.nat</i>	CAATCAAATCGAGTATT TTGTGACACAAATG		
	1120	1130	1140
<i>F.viral</i>	AACAGTTAACATTACCAAGTGAAGTAAAT		
<i>F.nat</i>	AACAGTTAACATTACCAAGTGAAGTAAAT		
	1150	1160	1170
<i>F.viral</i>	CTCTGCAATGTTGACATATTCAACCCAAAA		
<i>F.nat</i>	CTCTGCAATGTTGACATATTCAACCCAAAA		
	1180	1190	1200
<i>F.viral</i>	TATGATTGTAAAATTATGACTTCACAAACAA		
<i>F.nat</i>	TATGATTGTAAAATTATGACTTCACAAACAA		
	1210	1220	1230
<i>F.viral</i>	GATGTAAGCAGCTCCGTTATCACATCTCTA		
<i>F.nat</i>	GATGTAAGCAGCTCCGTTATCACATCTCTA		
	1240	1250	1260
<i>F.viral</i>	GGAGGCCATTGTGTCATGCTATGGCAAAACT		
<i>F.nat</i>	GGAGGCCATTGTGTCATGCTATGGCAAAACT		
	1270	1280	1290
<i>F.viral</i>	AAATGTACAGCATCCAAATAAAATCGTGGA		
<i>F.nat</i>	AAATGTACAGCATCCAAATAAAATCGTGGA		

Figure 6(iv)
SUBSTITUTE SHEET (RULE 26)

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	1300	1310	1320
<i>F.viral</i>	ATCATAAAGACATTTC	TAACCGGGTGC GAT	
<i>F.nat</i>	ATCATAAAGACATTTC	TAACCGGGTGC GAT	
	ATCATAAAGACATTTC	TAACCGGGTGC GAT	
	1330	1340	1350
<i>F.viral</i>	TATGTATCAAATAAAGGGGTTGGACACTGTG		
<i>F.nat</i>	TATGTATCAAATAAAGGGGTTGGACACTGTG		
	TATGTATCAAATAAAGGGGTTGGACACTGTG		
	1360	1370	1380
<i>F.viral</i>	TCTGTAGGTAAACACATTATATTATGTAAAT		
<i>F.nat</i>	TCTGTAGGTAAACACATTATATTATGTAAAT		
	TCTGTAGGTAAACACATTATATTATGTAAAT		
	1390	1400	1410
<i>F.viral</i>	AAGCAAGAACAGTAAAAGTCTCTATGTAAAT		
<i>F.nat</i>	AAGCAAGAACAGTAAAAGTCTCTATGTAAAT		
	AAGCAAGAACAGTAAAAGTCTCTATGTAAAT		
	1420	1430	1440
<i>F.viral</i>	GGTGAACCAATAATAATTTC	TATGACCCA	
<i>F.nat</i>	GGTGAACCAATAATAATTTC	TATGACCCA	
	GGTGAACCAATAATAATTTC	TATGACCCA	
	1450	1460	1470
<i>F.viral</i>	TTAGTATTCCCCCTGTGATGAATTTGATGCA		
<i>F.nat</i>	TTAGTATTCCCCCTGTGATGAATTTGATGCA		
	TTAGTATTCCCCCTGTGATGAATTTGATGCA		
	1480	1490	1500
<i>F.viral</i>	TCAATATCTCAAGTC	ACGAGAAAGATT AAC	
<i>F.nat</i>	TCAATATCTCAAGTC	ACGAGAAAGATT AAC	
	TCAATATCTCAAGTC	ACGAGAAAGATT AAC	
	1510	1520	1530
<i>F.viral</i>	CAGAGCCTAGCATTT	ATTCGTAATCCGAT	
<i>F.nat</i>	CAGAGCCTAGCATTT	ATTCGTAATCCGAT	
	CAGAGCCTAGCATTT	ATTCGTAATCCGAT	
	1540	1550	1560
<i>F.viral</i>	GAATTATTACATAATGT	AAATGCTGGT AAA	
<i>F.nat</i>	GAATTATTACATAATGT	AAATGCTGGT AAA	
	GAATTATTACATAATGT	AAATGCTGGT AAA	
	1570	1580	1590
<i>F.viral</i>	TCCACACCACAAATATC	ATGATAACTACTATA	
<i>F.nat</i>	TCCACACCACAAATATC	ATGATAACTACTATA	
	TCCACACCACAAATATC	ATGATAACTACTATA	
	1600	1610	1620
<i>F.viral</i>	ATTATAGTAGT GATTATAGTAATATTGTTATCA		
<i>F.nat</i>	ATTATAGTAGT GATTATAGTAATATTGTTATCA		
	ATTATAGTAGT GATTATAGTAATATTGTTATCA		

Figure 6(v)

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	1630	1640	1650
<i>F.viral</i>	TTAATTGCTGTTGGACTGCTCTTATACGT		
<i>F.nat</i>	TTAATTGCTGTTGGACTGCTCTTATACGT	TTAATTGCTGTTGGACTGCTCTTATACGT	
	1660	1670	1680
<i>F.viral</i>	AAGGCCAGAACGACACCCAGTCACACTAACG		
<i>F.nat</i>	AAGGCCAGAACGACACCCAGTCACACTAACG	AAGGCCAGAACGACACCCAGTCACACTAACG	
	1690	1700	1710
<i>F.viral</i>	AAAGATCAACTGAGTGGTATAAAATAATT		
<i>F.nat</i>	AAAGATCAACTGAGTGGTATAAAATAATT	AAAGATCAACTGAGTGGTATAAAATAATT	
	1720	1730	1740
<i>F.viral</i>	GCATTTAGTAAC TAA		
<i>F.nat</i>	GCATTAGTAAC TAA	GCATTAGTAAC TAA	

Figure 6(vi)
SUBSTITUTE SHEET (RULE 26)

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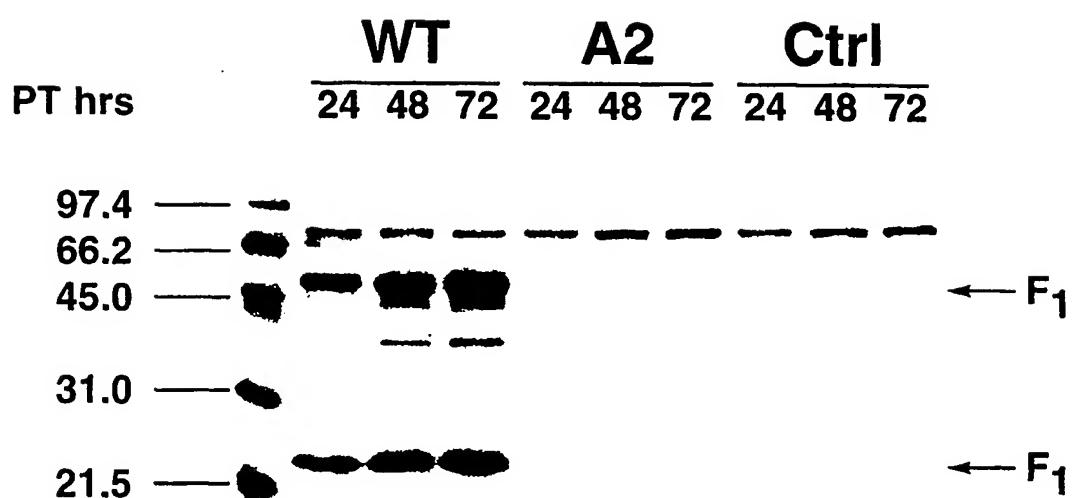


Figure 7
SUBSTITUTE SHEET (RULE 26)

40/40

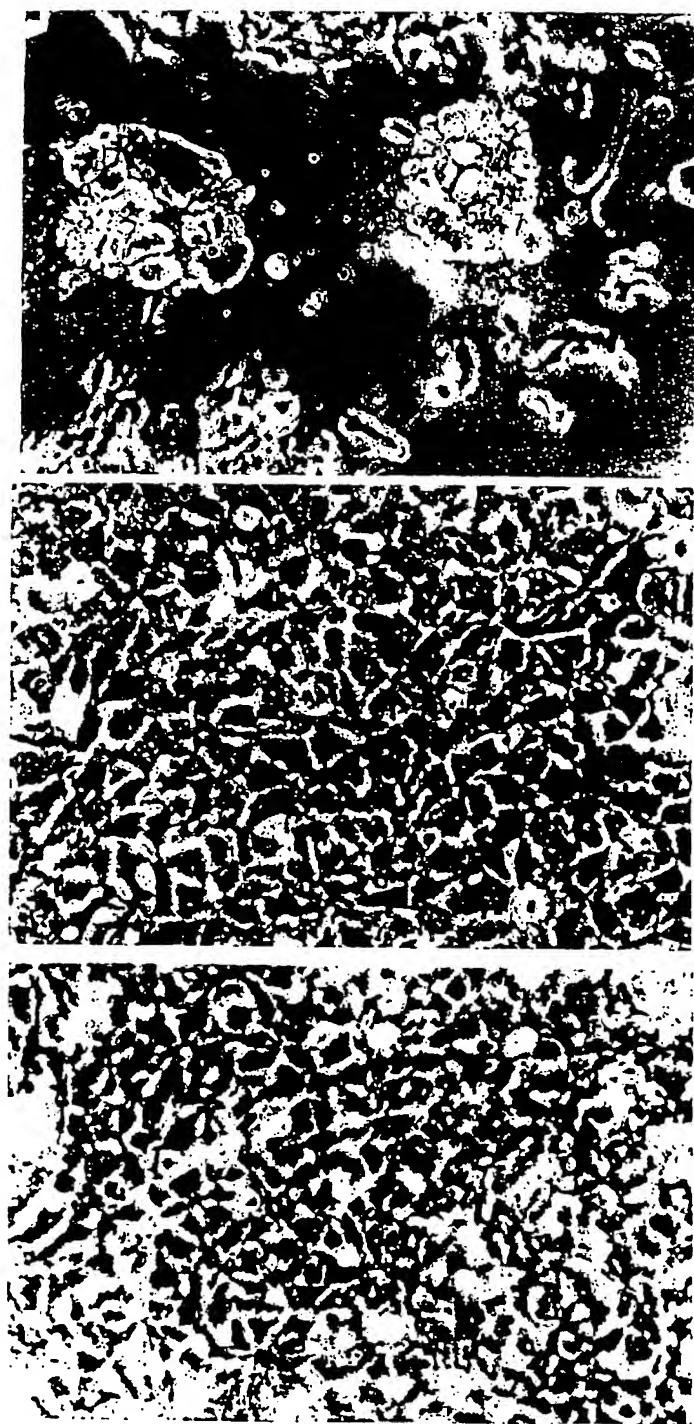


Figure 8
SUBSTITUTE SHEET (RULE 26)

- 1 -

SEQUENCE LISTING

<110> Biota Scientific Management Pty Ltd

<120> A method of expression and agents identified thereby

<130> 2479709/TDO

<140> International application

<141> 2001-11-22

<150> US 60/252767

<151> 2000-11-22

<160> 574

<170> PatentIn version 3.1

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- 5 -

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- 6 -

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tgttttgctt ctggtaaaaa catcaactgaa gaattttatc aatcaacatg cagtgcagtt 120
agcaaaggat atcttagtgc tctgagaacc ggttggata ccagtgttat aactatagaa 180
ttaagtaata tcaagaaaaa taagtgtat ggtaccgatg ctaaggtaaa attgataaaa 240

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caagaattag ataaatataa aaatgctgta acagaattgc agttgctcat gcagtcgaca	300
caagcaacaa acaatcgagc cagaagagaa ctacctaggt ttatgaatta tacactcaac	360
aatgccaaaa aaaccaatgt aacactttcg aagaaaagga aaagaagatt tcttggttt	420
ttgttaggtg ttggatccgc aatcgccagt ggcgttgctg tatctaaggc cctgcacatca	480
gagggggaag tgaacaagat caaaagtgc ctactatcca caaacaaggc tgtagtcagc	540
ttatcaaatg gagtttgtt cttaaccagc aaagtgttag acctcaaaaa ctatatacat	600
aaacaattgt tacctattgt gaacaagcaa agctgcagca tatcaaataat agaaactgtg	660
atagagttcc aacaaaagaa caacagacta cttagagatta ccagggatt tagtgttaat	720
gcaggtgtaa ctacacctgt aagcacttac atgttaacta atagtgaatt attgtcatta	780
atcaatgata tgcctataac aatgatcag aaaaagttaa tgtccaacaa tggtaataa	840
gttagacagc aaagtactc tatcatgtcc ataataaaag aggaagtctt agcatatgta	900
gtacaattac cactatatgg tgttatagat acaccctgtt ggaaactaca cacatcccct	960
ctatgtacaa ccaacacaaa agaagggtcc aacatctgtt taacaagaac tgacagagga	1020
tggtaactgtc acaatgcagg atcagttatct ttcttccac aagctgaaac atgtaaagtt	1080
caatcaaatc gagtatTTTg tgacacaatg aacagttaa cattaccaag tgaagtaat	1140
ctctgcaatg ttgacatatt caacccaaa tatgattgta aaattatgac ttcaaaaaca	1200
gatgtaaagca gctccgttat cacatctcta ggagccattg tgtcatgcta tggcaaaact	1260
aaatgtacag catccaataa aaatcggtt atcataaaga cattttctaa cgggtgcgt	1320
tatgtatcaa ataaagggtt ggacactgtg tctgttaggtt acacattata ttatgttaat	1380

- 8 -

aagcaagaag gtaaaagtct ctatgtaaaa ggtgaaccaa taataaattt ctatgaccca 1440
ttagtattcc cctctgatga atttgacgcg tcaatatctc aagtcaacga gaagattaac 1500
cagagcttag catttattcg taaatccgat gaattattac ataatgtaaa tgctggaaag 1560
agcaccacaa attaa 1575

<210> 5
<211> 1725
<212> DNA
<213> Artificial Sequence

<220>
<223> Optimised Sequence

<400> 5
atggagctgc tgatcctgaa ggccaacgcc atcaccacca tcctgaccgc ggtgaccttc 60
tgcttcgcct ctggccagaa catcaactgag gagttctacc agagcacttg ttccgctgtg 120
agcaagggct acctgagcgc cctgaggacc ggttggtaca ccagcgtgat caccatcgag 180
ctgagcaaca tcaagaagaa caagtgcAAC ggcacccgacg ccaagggtgaa gctgatcaag 240
caagagctgg acaagtacaa gaacgcccgtg accgagctgc aactgctgat gcagtcgact 300
caagccacca acaacagagc ccgcagagag ctgccccgt tcatgaacta caccctgaac 360
aacgccaaga agaccaacgt gaccctgtcc aagaagagga agcgccgctt cctgggcttc 420
ctgctgggcg tgggctccgc cattgccagt ggcgtggccg tgtccaagggt gctgcacctg 480
gagggcgagg tgaacaagat caagagtgcc ctgctgtcca ctaacaaggc cgtggtgagc 540
ctgagcaacg gcgtgagtgt gctgactagc aaggtgctgg acctgaagaa ctacatcgac 600

- 9 -

aagcaattgc tgcccatcgtaaacaaggcag tcctgttagca tctccaacat cgagactgtg 660
atcgagttcc agcagaagaa caaccgcctg ctggaaatca cccgggagtt cagtgtgaac 720
gctggcgtga ccactcctgt ctccacctac atgctgacca acagcgagct gctgagcctg 780
atcaacgaca tgcccatcac caacgaccag aagaagctta tgtccaacaa cgtgcagatc 840
gtgaggcagc agagctactc catcatgagc atcatcaagg aggaggtgct ggcctatgtg 900
gtgcagctgc ccctgtacgg cgtcatcgat accccttgct ggaagctgca caccagcccc 960
ctgtgcacca ccaacaccaa ggagggcagc aacatctgcc tgacccggac cgaccgcggc 1020
tggtaactgtg acaacgctgg ctcggtgagc ttcttcctc aagctgaaac ctgcaaggtc 1080
cagagcaaca gagtgttctg tgacaccatg aactccctga ccctgcccctc cgaggtgaac 1140
ctgtgcaacg tggatatctt caaccccaag tatgactgca agatcatgac ctccaagacc 1200
gatgtctcga gctccgtgat caccagcctg ggccgcattcg tggcttgcta tggcaagacc 1260
aagtgcaccc ccagcaaccaa gaaccggggc atcatcaaga cttcagcaa tgggtgcgac 1320
tacgtttcga acaagggcgt ggacactgtg tccgtggca acaccctgta ctacgtgaac 1380
aagcaagagg gcaagagcct gtatgtgaag ggccgcacca tcataactt ctacgacccc 1440
ctggtgttcc cctccgacga attcgacgcc tccattagcc aagtcaacga qaagatcaac 1500
cagagcctgg cttcatccg caagtccgac gagctgctgc acaacgtcaa cgctggcaag 1560
agcaccacca acatcatgat caccaccatc atcatcgta tcatacgat cctgctgagc 1620
ctgatcgccg tgggcctgct gctgtactgc aaggcccgaa gcactcccgat gaccctgagc 1680
aaggaccagc tgagcggcat caacaacatc gccttcagca actga 1725

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<210> 6
<211> 1575
<212> DNA
<213> Artificial Sequence

<220>
<223> Optimised Sequence

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tgcttcgcct ctggccagaa catcaactgag gagttctacc agagcacttg ttccgctgtg 120
agcaagggct acctgagcgc cctgaggacc ggttggtaca ccagcgtgat caccatcgag 180
ctgagcaaca tcaagaagaa caagtgcac ggcacccgacg ccaaggtgaa gctgatcaag 240
caagagctgg acaagtacaa gaacgcccgtg accgagctgc aactgctgat gcagtcgact 300
caagccacca acaacagagc cccgagagag ctgccccgt tcatgaacta caccctgaac 360
aacgccaaga agaccaacgt gaccctgtcc aagaagagga agcgccgctt cctgggcttc 420
ctgctggcg tgggctccgc cattgccagt ggcgtggccg tgtccaaggt gctgcacctg 480
gagggcgagg tgaacaagat caagagtgcc ctgctgtcca ctaacaaggc cgtggtgagc 540
ctgagcaacg gcgtgagtgt gctgactagc aagggtctgg acctgaagaa ctacatcgac 600
aagcaattgc tgcccatcgt gaacaaggcag tcctgttagca tctccaacat cgagactgtg 660
atcgagttcc agcagaagaa caaccgcctg ctggaaatca cccgggagtt cagtgtgaac 720
gctggcgtga ccactcctgt ctccacctac atgctgacca acagcgagct gctgagccctg 780
atcaacgaca tgcccatcac caacgaccag aagaagctta tgtccaacaa cgtgcagatc 840

- 11 -

gtgaggcagc agagctactc catcatgagc atcatcaagg aggaggtgct ggcctatgtg 900
gtgcagctgc ccctgtacgg cgtcatcgat accccttgct ggaagctgca caccagcccc 960
ctgtgcacca ccaacaccaa ggagggcagc aacatctgcc tgacccggac cgaccgcggc 1020
tggtaactgtg acaacgctgg ctccgtgagc ttcttcctc aagctgaaac ctgcaaggtc 1080
cagagcaaca gagtgttctg tgacaccatg aactccctga ccctgcccctc cgaggtgaac 1140
ctgtgcaacg tggatatctt caaccccaag tatgactgca agatcatgac ctccaagacc 1200
gatgtctcga gctccgtat caccagcctg ggcgcacatcg tgtcctgcta tggcaagacc 1260
aagtgcaccc ccagcaacaa gaaccggggc atcatcaaga cttcagcaa tgggtgcgac 1320
tacgtttcga acaagggcgt ggacactgtg tccgtggca acaccctgta ctacgtgaac 1380
aagcaagagg gcaagagcct gtatgtgaag ggcgagccca tcataactt ctacgacccc 1440
ctggtgttcc cctccgacga attcgacgca tccattagcc aagtcaacga gaagatcaac 1500
cagagcctgg cttcatccg caagtccgac gagctgctgc acaacgtcaa cgctggcaag 1560
agcaccacca actga 1575

<210> 7
<211> 574
<212> PRT
<213> respiratory syncytial virus

<400> 7

Met Glu Leu Leu Ile Leu Lys Ala Asn Ala Ile Thr Thr Ile Leu Thr
1 5 10 15

- 12 -

Ala Val Thr Phe Cys Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe
20 25 30

Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
35 40 45

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
50 55 60

Lys Lys Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
65 70 75 80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
85 90 95

Met Gln Ser Thr Gln Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro
100 105 110

Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr
115 120 125

Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
130 135 140

Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys Val Leu His Leu
145 150 155 160

Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys

- 13 -

165

170

175

Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
180 185 190

Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn
195 200 205

Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
210 215 220

Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
225 230 235 240

Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
245 250 255

Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys
260 265 270

Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
275 280 285

Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro
290 295 300

Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro
305 310 315 320

- 14 -

Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg
325 330 335

Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe
 340 345 350

Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp
355 360 365

Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val
370 375 380

Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr
 385 390 395 400

Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys
405 410 415

Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile
420 425 430

Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp
 435 440 445

Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly
450 455 460

Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro

- 15 -

465 470 475 . 480

485 490 495

Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu

500 505 510

Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr

515 520 525

Thr Ile Ile Ile Val Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val

530 535 540

Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser

545 **550** **555** **560**

Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala Phe Ser Asn

565 570

<210> 8

<211> 524

<212> PRT

<213> respiratory syncytial virus

<400> 8

Met Glu Leu Leu Ile Leu Lys Ala Asp Ala Ile Thr Thr Thr Ile Leu Thr

1 5 10 15

- 16 -

Ala Val Thr Phe Cys Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe
20 25 30

Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
35 40 45

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
50 55 60

Lys Lys Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
65 70 75 80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
85 90 95

Met Gln Ser Thr Gln Ala Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro
100 105 110

Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr
115 120 125

Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
130 135 140

Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys Val Leu His Leu
145 150 155 160

Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
165 170 175

- 17 -

Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
180 185 190

Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn
195 200 205

Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
210 215 220

Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
225 230 235 240

Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
245 250 255

Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys
260 265 270

Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
275 280 285

Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro
290 295 300

Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro
305 310 315 320

- 18 -

Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg
 325 330 335

Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe
 340 345 350

Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp
355 360 365

Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val
370 375 380

Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr
385 390 395 400

Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys
405 410 415

Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile
 420 425 430

Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp
 435 440 . 445

Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly
450 455 460

Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro
 465 470 475 480

- 19 -

Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn
485 490 495

Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu
500 505 510

Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn
515 520

<210> 9
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 9

Cys Phe Ala Ser Gly Gln Asn Ile Thr Glu
1 5 10

<210> 10
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 10

Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu
1 5 10

<210> 11
<211> 10

- 20 -

<212> PRT
<213> respiratory syncytial virus

<400> 11

Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe
1 5 10

<210> 12
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 12

Ser Gly Gln Asn Ile Thr Glu Glu Phe Tyr
1 5 10

<210> 13
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 13

Gly Gln Asn Ile Thr Glu Glu Phe Tyr Gln
1 5 10

<210> 14
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 14

- 21 -

Gln Asn Ile Thr Glu Glu Phe Tyr Gln Ser
1 5 10

<210> 15
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 15

Asn Ile Thr Glu Glu Phe Tyr Gln Ser Thr
1 5 10

<210> 16
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 16

Ile Thr Glu Glu Phe Tyr Gln Ser Thr Cys
1 5 10

<210> 17
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 17

Thr Glu Glu Phe Tyr Gln Ser Thr Cys Ser
1 5 10

<210> 18

- 22 -

<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 18

Glu Glu Phe Tyr Gln Ser Thr Cys Ser Ala
1 5 10

<210> 19
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 19

Glu Phe Tyr Gln Ser Thr Cys Ser Ala Val
1 5 10

<210> 20
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 20

Phe Tyr Gln Ser Thr Cys Ser Ala Val Ser
1 5 10

<210> 21
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 21

- 23 -

Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys
1 5 10

<210> 22
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 22

Gln Ser Thr Cys Ser Ala Val Ser Lys Gly
1 5 10

<210> 23
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 23

Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr
1 5 10

<210> 24
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 24

Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu
1 5 10

- 24 -

<210> 25
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 25

Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser
1 5 10

<210> 26
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 26

Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala
1 5 10

<210> 27
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 27

Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
1 5 10

<210> 28
<211> 10
<212> PRT
<213> respiratory syncytial virus

- 25 -

<400> 28

Val Ser Lys Gly Tyr Leu Ser Ala Leu Arg
1 5 10

<210> 29

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 29

Ser Lys Gly Tyr Leu Ser Ala Leu Arg Thr
1 5 10

<210> 30

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 30

Lys Gly Tyr Leu Ser Ala Leu Arg Thr Gly
1 5 10 .

<210> 31

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 31

Gly Tyr Leu Ser Ala Leu Arg Thr Gly Trp
1 5 10

- 26 -

<210> 32
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 32

Tyr Leu Ser Ala Leu Arg Thr Gly Trp Tyr
1 5 10

<210> 33
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 33

Leu Ser Ala Leu Arg Thr Gly Trp Tyr Thr
1 5 10

<210> 34
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 34

Ser Ala Leu Arg Thr Gly Trp Tyr Thr Ser
1 5 10

<210> 35
<211> 10
<212> PRT
<213> respiratory syncytial virus

- 27 -

<400> 35

Ala Leu Arg Thr Gly Trp Tyr Thr Ser Val
1 5 10

<210> 36

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 36

Leu Arg Thr Gly Trp Tyr Thr Ser Val Ile
1 5 10

<210> 37

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 37

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr
1 5 10

<210> 38

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 38

Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile
1 5 . 10

- 28 -

<210> 39
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 39

Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu
1 5 10

<210> 40
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 40

Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu
1 5 10

<210> 41
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 41

Thr Ser Val Ile Thr Ile Glu Leu Ser Asn
1 5 10

<210> 42
<211> 10
<212> PRT

- 29 -

<213> respiratory syncytial virus

<400> 42

Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
1 5 10

<210> 43

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 43

Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
1 5 10

<210> 44

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 44

Val Ile Thr Ile Glu Leu Ser Asn Ile Lys
1 5 10

<210> 45

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 45

Ile Thr Ile Glu Leu Ser Asn Ile Lys Lys

- 30 -

1 5 10

<210> 46
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 46

Thr Ile Glu Leu Ser Asn Ile Lys Lys Asn
1 5 10

<210> 47
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 47

Ile Glu Leu Ser Asn Ile Lys Lys Asn Lys
1 5 10

<210> 48
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 48

Glu Leu Ser Asn Ile Lys Lys Asn Lys Cys
1 5 10

<210> 49
<211> 10

- 31 -

<212> PRT

<213> respiratory syncytial virus

<400> 49

Leu Ser Asn Ile Lys Lys Asn Lys Cys Asn

1 5 10

<210> 50

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 50

Ser Asn Ile Lys Lys Asn Lys Cys Asn Gly

1 5 10

<210> 51

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 51

Asn Ile Lys Lys Asn Lys Cys Asn Gly Thr

1 5 10

<210> 52

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 52

- 32 -

Ile Lys Lys Asn Lys Cys Asn Gly Thr Asp
1 5 10

<210> 53
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 53

Lys Lys Asn Lys Cys Asn Gly Thr Asp Ala
1 5 10

<210> 54
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 54

Lys Asn Lys Cys Asn Gly Thr Asp Ala Lys
1 5 10

<210> 55
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 55

Asn Lys Cys Asn Gly Thr Asp Ala Lys Val
1 5 10

<210> 56

- 33 -

<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 56

Lys Cys Asn Gly Thr Asp Ala Lys Val Lys
1 5 10

<210> 57
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 57

Cys Asn Gly Thr Asp Ala Lys Val Lys Leu
1 5 10

<210> 58
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 58

Asn Gly Thr Asp Ala Lys Val Lys Leu Ile
1 5 10

<210> 59
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 59

- 34 -

Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
1 5 10

<210> 60
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 60

Thr Asp Ala Lys Val Lys Leu Ile Lys Gln
1 5 10

<210> 61
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 61

Asp Ala Lys Val Lys Leu Ile Lys Gln Glu
1 5 10

<210> 62
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 62

Ala Lys Val Lys Leu Ile Lys Gln Glu Leu
1 5 10

- 35 -

<210> 63
<211> 10
<212> PRT
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<400> 63

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Leu Ile Lys Gln Glu Leu Asp Lys Tyr Lys
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Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val
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Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu
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Asn Asn Arg Ala Arg Arg Glu Leu Pro Arg
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Asn Arg Ala Arg Arg Glu Leu Pro Arg Phe
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Arg Ala Arg Arg Glu Leu Pro Arg Phe Met
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Ala Arg Arg Glu Leu Pro Arg Phe Met Asn
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Arg Arg Glu Leu Pro Arg Phe Met Asn Tyr
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Arg Glu Leu Pro Arg Phe Met Asn Tyr Thr
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Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys
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Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys
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Thr Asn Val Thr Leu Ser Lys Lys Arg Lys
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Arg Phe Leu Gly Phe Leu Leu Gly Val Gly
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Gly Phe Leu Leu Gly Val Gly Ser Ala Ile
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Phe Leu Leu Gly Val Gly Ser Ala Ile Ala
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Gly Ser Ala Ile Ala Ser Gly Val Ala Val

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Val Ala Val Ser Lys Val Leu His Leu Glu
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Ser Lys Val Leu His Leu Glu Gly Glu Val
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His Leu Glu Gly Glu Val Asn Lys Ile Lys
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Val Leu Thr Ser Lys Val Leu Asp Leu Lys
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Leu Thr Ser Lys Val Leu Asp Leu Lys Asn
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Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile
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Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val
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Pro Ile Val Asn Lys Gln Ser Cys Ser Ile
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Val Asn Lys Gln Ser Cys Ser Ile Ser Asn
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Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu

- 74 -

1 5 10

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Glu Thr Val Ile Glu Phe Gln Gln Lys Asn
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Thr Val Ile Glu Phe Gln Gln Lys Asn Asn
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Val Ile Glu Phe Gln Gln Lys Asn Asn Arg
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Arg Glu Phe Ser Val Asn Ala Gly Val Thr
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Glu Phe Ser Val Asn Ala Gly Val Thr Thr
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Val Ser Thr Tyr Met Leu Thr Asn Ser Glu

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Asp Met Pro Ile Thr Asn Asp Gln Lys Lys
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Met Ser Asn Asn Val Gln Ile Val Arg Gln
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Val Arg Gln Gln Ser Tyr Ser Ile Met Ser
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Ser Tyr Ser Ile Met Ser Ile Ile Lys Glu

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Glu Glu Val Leu Ala Tyr Val Val Gln Leu
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Glu Val Leu Ala Tyr Val Val Gln Leu Pro
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Tyr Val Val Gln Leu Pro Leu Tyr Gly Val
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Val Gln Leu Pro Leu Tyr Gly Val Ile Asp
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Pro Leu Tyr Gly Val Ile Asp Thr Pro Cys
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Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp
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Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys
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Gly Val Ile Asp Thr Pro Cys Trp Lys Leu
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Val Ile Asp Thr Pro Cys Trp Lys Leu His
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Ile Asp Thr Pro Cys Trp Lys Leu His Thr
1 5 10

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Asp Thr Pro Cys Trp Lys Leu His Thr Ser
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Thr Pro Cys Trp Lys Leu His Thr Ser Pro
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Lys Leu His Thr Ser Pro Leu Cys Thr Thr
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Leu His Thr Ser Pro Leu Cys Thr Thr Asn
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Ser Asn Ile Cys Leu Thr Arg Thr Asp Arg
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Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala
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Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser
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Asp Asn Ala Gly Ser Val Ser Phe Phe Pro
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Ala Gly Ser Val Ser Phe Phe Pro Gln Ala
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Val Ser Phe Phe Pro Gln Ala Glu Thr Cys
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Glu Thr Cys Lys Val Gln Ser Asn Arg Val
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Lys Val Gln Ser Asn Arg Val Phe Cys Asp
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Val Gln Ser Asn Arg Val Phe Cys Asp Thr
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Gln Ser Asn Arg Val Phe Cys Asp Thr Met

- 118 -

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Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn
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Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro
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Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile
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Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser
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Asp Ala Ser Ile Ser Gln Val Asn Glu Lys
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Val Asn Glu Lys Ile Asn Gln Ser Leu Ala
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Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg
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Lys Ser Asp Glu Leu Leu His Asn Val Asn
1 5 10

<210> 497
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 497

Ser Asp Glu Leu Leu His Asn Val Asn Ala
1 5 10

<210> 498
<211> 10
<212> PRT

- 161 -

<213> respiratory syncytial virus

<400> 498

Asp Glu Leu Leu His Asn Val Asn Ala Gly
1 5 10

<210> 499

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 499

Glu Leu Leu His Asn Val Asn Ala Gly Lys
1 5 10

<210> 500

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 500

Leu Leu His Asn Val Asn Ala Gly Lys Ser
1 5 10

<210> 501

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 501

Leu His Asn Val Asn Ala Gly Lys Ser Thr

- 162 -

1 5 10

<210> 502
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 502

His Asn Val Asn Ala Gly Lys Ser Thr Thr
1 5 10

<210> 503
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 503

Asn Val Asn Ala Gly Lys Ser Thr Thr Asn
1 5 10

<210> 504
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 504

Val Asn Ala Gly Lys Ser Thr Thr Asn Ile
1 5 10

<210> 505
<211> 10

- 163 -

<212> PRT

<213> respiratory syncytial virus

<400> 505

Asn Ala Gly Lys Ser Thr Thr Asn Ile Met
1 5 10

<210> 506

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 506

Ala Gly Lys Ser Thr Thr Asn Ile Met Ile
1 5 10

<210> 507

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 507

Gly Lys Ser Thr Thr Asn Ile Met Ile Thr
1 5 10

<210> 508

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 508

- 164 -

Lys Ser Thr Thr Asn Ile Met Ile Thr Thr
1 5 10

<210> 509
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 509

Ser Thr Thr Asn Ile Met Ile Thr Thr Ile
1 5 10

<210> 510
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 510

Thr Thr Asn Ile Met Ile Thr Thr Ile Ile
1 5 10

<210> 511
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 511

Thr Asn Ile Met Ile Thr Thr Ile Ile Ile
1 5 10

<210> 512

- 165 -

<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 512

Asn Ile Met Ile Thr Thr Ile Ile Ile Val
1 5 10

<210> 513
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 513

Ile Met Ile Thr Thr Ile Ile Ile Val Ile
1 5 10

<210> 514
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 514

Met Ile Thr Thr Ile Ile Ile Val Ile Ile
1 5 10

<210> 515
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 515

- 166 -

Ile Thr Thr Ile Ile Ile Val Ile Ile Val
1 5 10

<210> 516
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 516

Thr Thr Ile Ile Ile Val Ile Ile Val Ile
1 5 10

<210> 517
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 517

Thr Ile Ile Ile Val Ile Ile Val Ile Leu
1 5 10

<210> 518
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 518

Ile Ile Ile Val Ile Ile Val Ile Leu Leu
1 5 10

- 167 -

<210> 519
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 519

Ile Ile Val Ile Ile Val Ile Leu Leu Ser
1 5 10

<210> 520
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 520

Ile Val Ile Ile Val Ile Leu Leu Ser Leu
1 5 10

<210> 521
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 521

Val Ile Ile Val Ile Leu Leu Ser Leu Ile
1 5 10

<210> 522
<211> 10
<212> PRT
<213> respiratory syncytial virus

- 168 -

<400> 522

Ile Ile Val Ile Leu Leu Ser Leu Ile Ala
1 5 10

<210> 523

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 523

Ile Val Ile Leu Leu Ser Leu Ile Ala Val
1 5 10

<210> 524

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 524

Val Ile Leu Leu Ser Leu Ile Ala Val Gly
1 5 10

<210> 525

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 525

Ile Leu Leu Ser Leu Ile Ala Val Gly Leu
1 5 10

- 169 -

<210> 526
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 526

Leu Leu Ser Leu Ile Ala Val Gly Leu Leu
1 5 10

<210> 527
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 527

Leu Ser Leu Ile Ala Val Gly Leu Leu Leu
1 5 10

<210> 528
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 528

Ser Leu Ile Ala Val Gly Leu Leu Tyr
1 5 10

<210> 529
<211> 10
<212> PRT
<213> respiratory syncytial virus

- 170 -

<400> 529

Leu Ile Ala Val Gly Leu Leu Leu Tyr Cys
1 5 10

<210> 530

<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 530

Ile Ala Val Gly Leu Leu Leu Tyr Cys Lys
1 5 10

<210> 531

<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 531

Ala Val Gly Leu Leu Leu Tyr Cys Lys Ala
1 5 10

<210> 532

<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 532

Val Gly Leu Leu Leu Tyr Cys Lys Ala Arg
1 5 10

- 171 -

<210> 533
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 533

Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser
1 5 10

<210> 534
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 534

Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr
1 5 10

<210> 535
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 535

Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro
1 5 10

<210> 536
<211> 10
<212> PRT

- 172 -

<213> respiratory syncytial virus

<400> 536

Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val
1 5 10

<210> 537

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 537

Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr
1 5 10

<210> 538

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 538

Cys Lys Ala Arg Ser Thr Pro Val Thr Leu
1 5 10

<210> 539

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 539

Lys Ala Arg Ser Thr Pro Val Thr Leu Ser

- 173 -

1 5 10

<210> 540
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 540

Ala Arg Ser Thr Pro Val Thr Leu Ser Lys
1 5 10

<210> 541
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 541

Arg Ser Thr Pro Val Thr Leu Ser Lys Asp
1 5 10

<210> 542
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 542

Ser Thr Pro Val Thr Leu Ser Lys Asp Gln
1 5 10

<210> 543
<211> 10

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<212> PRT

<213> respiratory syncytial virus

<400> 543

Thr Pro Val Thr Leu Ser Lys Asp Gln Leu
1 5 10

<210> 544

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 544

Pro Val Thr Leu Ser Lys Asp Gln Leu Ser
1 5 10

<210> 545

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 545

Val Thr Leu Ser Lys Asp Gln Leu Ser Gly
1 5 10

<210> 546

<211> 10

<212> PRT

<213> respiratory syncytial virus

<400> 546

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Thr Leu Ser Lys Asp Gln Leu Ser Gly Ile
1 5 10

<210> 547
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 547

Leu Ser Lys Asp Gln Leu Ser Gly Ile Asn
1 5 10

<210> 548
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 548

Ser Lys Asp Gln Leu Ser Gly Ile Asn Asn
1 5 10

<210> 549
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 549

Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile
1 5 10

<210> 550

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<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 550

Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala
1 5 10

<210> 551
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 551

Gln Leu Ser Gly Ile Asn Asn Ile Ala Phe
1 5 10

<210> 552
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 552

Leu Ser Gly Ile Asn Asn Ile Ala Phe Ser
1 5 10

<210> 553
<211> 10
<212> PRT
<213> respiratory syncytial virus

<400> 553

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Ser Gly Ile Asn Asn Ile Ala Phe Ser Asn

1 5 10

<210> 554

<211> 241

<212> PRT

<213> respiratory syncytial virus

<400> 554

Met Glu Lys Phe Ala Pro Glu Phe His Gly Glu Asp Ala Asn Asn Arg

1 5 10 15

Ala Thr Lys Phe Leu Glu Ser Ile Lys Gly Lys Phe Thr Ser Pro Lys

20 25 30

Asp Pro Lys Lys Asp Ser Ile Ile Ser Val Asn Ser Ile Asp Ile

35 40 45

Glu Val Thr Lys Glu Ser Pro Ile Thr Ser Asn Ser Thr Ile Ile Asn

50 55 60

Pro Thr Asn Glu Thr Asp Asp Thr Ala Gly Asn Lys Pro Asn Tyr Gln

65 70 75 80

Arg Lys Pro Leu Val Ser Phe Lys Glu Asp Pro Thr Pro Ser Asp Asn

85 90 95

Pro Phe Ser Lys Leu Tyr Lys Glu Thr Ile Glu Thr Phe Asp Asn Asn

100 105 110

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Glu Glu Glu Ser Ser Tyr Ser Tyr Glu Glu Ile Asn Asp Gln Thr Asn
115 120 125

Asp Asn Ile Thr Ala Arg Leu Asp Arg Ile Asp Glu Lys Leu Ser Glu
130 135 140

Ile Leu Gly Met Leu His Thr Leu Val Val Ala Ser Ala Gly Pro Thr
145 150 155 160

Ser Ala Arg Asp Gly Ile Arg Asp Ala Met Ile Gly Leu Arg Glu Glu
165 170 175

Met Ile Glu Lys Ile Arg Thr Glu Ala Leu Met Thr Asn Asp Arg Leu
180 185 190

Glu Ala Met Ala Arg Leu Arg Asn Glu Glu Ser Glu Lys Met Ala Lys
195 200 205

Asp Thr Ser Asp Glu Val Ser Leu Asn Pro Thr Ser Glu Lys Leu Asn
210 215 220

Asn Leu Leu Glu Gly Asn Asp Ser Asp Asn Asp Leu Ser Leu Glu Asp
225 230 235 240

Phe

- 179 -

<210> 555
<211> 726
<212> DNA
<213> *respiratory syncytial virus*

<400> 555

atggaaaagt ttgctcctga attccatgga gaagatgcaa acaacaggc tactaaattc 60
ctagaatcaa taaaggcaa attcacatca cccaaagatc ccaagaaaaa agatagtatc 120
atatctgtca actcaataga tatagaagta accaaagaaa gccctataac atcaaattca 180
actattatca acccaacaaa tgagacagat gatactgcag ggaacaagcc caattatcaa 240
agaaaaacctc tagtaagttt caaagaagac cctacaccaa gtgataatcc ctttctaaa 300
ctatacaaag aaaccataga aacatttgat aacaatgaag aagaatccag ctattcatac 360
gaagaaataa atgatcagac aaacgataat ataacagcaa gattagatag gattgatgaa 420
aaattaagtg aaatactagg aatgcttcac acatttagtag tggcaagtgc aggacctaca 480
tctgctcggg atggataag agatgccatg attggttaa gagaágaaat gatagaaaaa 540
atcagaactg aagcattaat gaccaatgac agattagaag ctatggcaag actcaggaat 600
gaggaaagtg aaaagatggc aaaagacaca tcagatgaag tgtctctcaa tccaacatca 660
gagaaattga acaacctatt ggaaggaaat gatagtgaca atgatctatc acttgaagat 720
ttctgta 726

<210> 556
<211> 726
<212> DNA
<213> Artificial Sequence

- 180 -

<220>

<223> Optimised Sequence

<400> 556

atggagaagt tcgccccga gttccacggc gaggacgcca acaatcgccc caccaagttc 60
ctggagagca tcaagggcaa gttcaccagc cccaggacc ccaagaaaaa ggacagcattc 120
atcccggtga acagcatcga catcgagggt accaaggaga gccccatcac ctccaaacagc 180
accatcatcata accccaccaa cgagacagac gataccgccc gcaacaagcc caactaccag 240
cggaagcccc tggtagctt caaggaggac cccaccccta ggcacaaccc cttcagcaag 300
ctgtacaagg agaccatcga gacccatcgac aacaatgagg aagagagctc ctacagctac 360
gaagagatca acgaccagac caacgacaac atcaccgccc ggctggacag aatcgacgag 420
aagctgagcg agatcctggg catgctgcac accctgggtgg tcgcccagcgc cggccccacc 480
agcgccccggg acggcatcag agacgcccattg atcggcctgc gggaggaaat gatcgagaag 540
atccggacccg aggccctgat gaccaacgac cggctggagg ctatggccag actgcggaac 600
gaggaaagcg agaagatggc caaggacacc agcgacgagg tgagcctgaa cccaccaggc 660
gagaagctga acaatctgct cgagggcaac gacagcgata acgacctgag cctggaggac 720
ttctgt 726

<210> 557

<211> 391

<212> PRT

<213> respiratory syncytial virus

<400> 557

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Met Ala Leu Ser Lys Val Lys Leu Asn Asp Thr Leu Asn Lys Asp Gln

1 5 10 15

Leu Leu Ser Ser Ser Lys Tyr Thr Ile Gln Arg Ser Thr Gly Asp Ser

20 25 30

Ile Asp Thr Pro Asn Tyr Asp Val Gln Lys His Ile Asn Lys Leu Cys

35 40 45

Gly Met Leu Leu Ile Thr Glu Asp Ala Asn His Lys Phe Thr Gly Leu

50 55 60

Ile Gly Met Leu Tyr Ala Met Ser Arg Leu Gly Arg Glu Asp Thr Ile

65 70 75 80

Lys Ile Leu Arg Asp Ala Gly Tyr His Val Lys Ala Asn Gly Val Asp

85 90 95

Val Thr Thr His Arg Gln Asp Ile Asn Gly Lys Glu Met Lys Phe Glu

100 105 110

Val Leu Thr Leu Ala Ser Leu Thr Thr Glu Ile Gln Ile Asn Ile Glu

115 120 125

Ile Glu Ser Arg Lys Ser Tyr Lys Lys Met Leu Lys Glu Met Gly Glu

130 135 140

Val Ala Pro Glu Tyr Arg His Asp Ser Pro Asp Cys Gly Met Ile Ile

145 150 155 160

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Leu Cys Ile Ala Ala Leu Val Ile Thr Lys Leu Ala Ala Gly Asp Arg
165 170 175

Ser Gly Leu Thr Ala Val Ile Arg Arg Ala Asn Asn Val Leu Lys Asn
180 185 190

Glu Met Lys Arg Tyr Lys Gly Leu Leu Pro Lys Asp Ile Ala Asn Ser
195 200 205

Phe Tyr Glu Val Phe Glu Lys His Pro His Phe Ile Asp Val Phe Val
210 215 220

His Phe Gly Ile Ala Gln Ser Ser Thr Arg Gly Gly Ser Arg Val Glu
225 230 235 240

Gly Ile Phe Ala Gly Leu Phe Met Asn Ala Tyr Gly Ala Gly Gln Val
245 250 255

Met Leu Arg Trp Gly Val Leu Ala Lys Ser Val Lys Asn Ile Met Leu
260 265 270

Gly His Ala Ser Val Gln Ala Glu Met Glu Gln Val Val Glu Val Tyr
275 280 285

Glu Tyr Ala Gln Lys Leu Gly Gly Glu Ala Gly Phe Tyr His Ile Leu
290 295 300

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Asn Asn Pro Lys Ala Ser Leu Leu Ser Leu Thr Gln Phe Pro His Phe
305 310 315 320

Ser Ser Val Val Leu Gly Asn Ala Ala Gly Leu Gly Ile Met Gly Glu
325 330 335

Tyr Arg Gly Thr Pro Arg Asn Gln Asp Leu Tyr Asp Ala Ala Lys Ala
340 345 350

Tyr Ala Glu Gln Leu Lys Glu Asn Gly Val Ile Asn Tyr Ser Val Leu
355 360 365

Asp Leu Thr Ala Glu Glu Leu Glu Ala Ile Lys His Gln Leu Asn Pro
370 375 380

Lys Asp Asn Asp Val Glu Leu
385 390

<210> 558
<211> 1176
<212> DNA
<213> respiratory syncytial virus

<400> 558
atggcttta gcaaagtcaa gttgaatgat acactcaaca aagatcaact tctgtcatcc 60

agcaaataca ccatccaacg gagcacagga gatagtattg atactcctaa ttatgtgtg 120

cagaaaacaca tcaataagtt atgtggcatg ttattaatca cagaagatgc taatcataaa 180

ttcactgggt taataggtat gtttatatgcg atgtctaggt taggaagaga agacaccata 240

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aaaatactca gagatgcggg atatcatgt aagcaaatg gagtagatgt aacaacacat 300
cgtcaagaca ttaatggaaa agaaatgaaa ttgaagtgt taacattggc aagcttaaca 360
actgaaattc aaatcaacat tgagatagaa tctagaaaaat cctacaaaaa aatgctaaaa 420
gaaatgggag agtagtcc agaatacagg catgactctc ctgattgtgg gatgataata 480
ttatgtatag cagcattagt aataactaaa ttagcagcag gggacagatc tggtcttaca 540
. gccgtgatta ggagagctaa taatgtccta aaaaatgaaa taaaacgtta caaaggctta 600
ctacccaagg acatagccaa cagcttctat gaagtgtttg aaaaacatcc ccactttata 660
gatgttttg ttcattttgg tatagcacaa tcttctacca gaggtggcag tagagttgaa 720
gggattttg caggattgtt tatgaatgcc tatggcag ggcaagtgtat gttacggcgg 780
ggagtcttag caaatcagt taaaatatt atgttaggac atgctagtgt gcaacgcagaa 840
atggaacaag ttgttgaggt ttatgaatat gccaaaaat tgggtggtga agcaggattc 900
taccatatat tgaacaaccc aaaagcatca ttattatctt tgactcaatt tcctcacttc 960
tccagtgttag tattaggcaa tgctgctggc ctaggcataa tgggagagta cagaggtaca 1020
ccgaggaatc aagatctata tgatgcagca aaggcatatg ctgaacaact caaagaaaaat 1080
ggtgtgatta actacagtgt actagacttg acagcagaag aactagaggc tatcaaacat 1140
cagcttaatc caaaagataa tgatgttagag ctggta 1176

<210> 559

<211> 1176

<212> DNA

<213> Artificial Sequence

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<220>

<223> Optimised Sequence

<400> 559

atggccctga gcaagggtgaa actcaacgac accctgaata aggatcagct cctgagctcc 60
tctaaataca ccatccagcg gagcaccggc gacagcattg ataccccaa ctacgacgtg 120
cagaaggcaca tcaacaaaact gtgcggcatg ctcctgatca ccgaggacgc caaccacaag 180
ttcacccggcc tgatcgggat gctctacgcc atgagccggc tgggcagaga ggacaccatc 240
aagattctgc gggatgccgg ctaccacgtg aaggccaacg gagtcgacgt gaccacacac 300
cggcaggata tcaacggcaa ggagatgaaa ttcgaagtgc tgaccctcgc cagcctgaca 360
accgagatcc agattaacat cgaaatttag tcccggaga gctacaaaaa gatgctgaaa 420
gagatggcg aagtggcccc cgagtaccgg cacgacagcc ccgattgcgg catgatcatt 480
ctgtgtatcg ccgctctcg tattaccaag ctggccgctg gcgaccggag cgggctgacc 540
gccgtgatca gacgggctaa caatgtgctg aagaacgaga taaaacggta caagggctc 600
ctgccccaaag acatgccaa cagttctac gaggtgtttg aaaagcaccc ccatttcattc 660
gacgtctttg tgcacttcgg cattgcccag agctccacca gaggcgggag ccgggtggag 720
ggcatcttcg ccgggctgtt tatgaacgct tacggcgccg ggcaggtgat gctgcggtg 780
ggcgtcctcg ccaagagcgt gaaaaacatc atgctggcc acgccagcgt gcaggctgag 840
atgaaacaag tggtcgaggt gtacgaatat gcccagaagc tggcggaga ggctggcttc 900
taccacatcc tgaacaatcc caaggccagc ctcctgtccc tcacccagtt tccccacttc 960
agctccgtcg tgctggcaa cgccgctgga ctcgggatca tggcggatca ccggggaaacc 1020

- 186 -

cccagaaaacc aggacctgta tgatgccgt aaggcatacg ccgagcagct gaaagaaaac 1080

ggcgtgatca attacagcgt gctggacctc accgcccagg aactggaggc tatcaagcac 1140

cagctcaacc ccaaagacaa tgatgtggag ctgtga 1176

<210> 560

<211> 64

<212> PRT

<213> respiratory syncytial virus

<400> 560

Met Glu Asn Thr Ser Ile Thr Ile Glu Phe Ser Ser Lys Phe Trp Pro

1

5

10

15

Tyr Phe Thr Leu Ile His Met Ile Thr Thr Ile Ile Ser Leu Leu Ile

20

25

30

Ile Ile Ser Ile Met Ile Ala Ile Leu Asn Lys Leu Cys Glu Tyr Asn

35

40

45

Val Phe His Asn Lys Thr Phe Glu Leu Pro Arg Ala Arg Val Asn Thr

50

55

60

<210> 561

<211> 195

<212> DNA

<213> respiratory syncytial virus

<400> 561

atggaaaaata catccataaac aatagaattc tcaagcaaat tctggcctta ctttacacta 60

- 187 -

atacacatga tcacaacaat aatctctttg ctaatcataa tctccatcat gattgcaata 120

ctaaacaaac tttgtgaata taacgtattc cataacaaaa cctttgagtt accaagagct 180

cgagtcaaca catag 195

<210> 562

<211> 195

<212> DNA

<213> Artificial Sequence

<220>

<223> Optimised sequence

<400> 562

atggagaaca cctccatcac cattgagttc tcctccaagt tctggccata cttcacccctg 60

atccacatga tcaccacccat catctccctg ctgatcatca tctccatcat gattgccatc 120

ctgaacaaggc tttgtgagta caatgtcttc cacaacaaga cctttgagct gccccggcc 180

cgggtgaaca cctga 195

<210> 563

<211> 6

<212> PRT

<213> respiratory syncytial virus

<400> 563

Lys Lys Arg Lys Arg Arg

1

5

<210> 564

<211> 4

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<212> PRT
<213> respiratory syncytial virus

<400> 564

Arg Ala Arg Arg
1

<210> 565
<211> 575
<212> PRT
<213> Artificial Sequence

<220>
<223> RSV F Protein Variant

<220>
<221> MISC_FEATURE
<222> (575)..(575)
<223> Xaa is any nucleotide

<400> 565

Met Glu Leu Leu Ile Leu Lys Ala Asn Ala Ile Thr Thr Ile Leu Thr
1 5 10 15

Ala Val Thr Phe Cys Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe
20 25 30

Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
35 40 45

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile

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50 55 60

Lys Lys Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
65 70 75 80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
85 90 95

Met Gln Ser Thr Gln Ala Thr Asn Asn Gly Gln Gly Arg Glu Leu Pro
100 105 110

Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr
115 120 125

Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
130 135 140

Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys Val Leu His Leu
145 150 155 160

Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
165 170 175

Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
180 185 190

Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn
195 200 205

- 190 -

Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
210 215 220

Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
225 230 235 240

Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
245 250 255

Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys
260 265 270

Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
275 280 285

Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro
290 295 300

Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro
305 310 315 320

Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg
325 330 335

Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe
340 345 350

Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp

- 191 -

355

360

365

Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val
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Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr
385 390 395 400

Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys
405 410 415

Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile
420 425 430

Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp
435 440 445

Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly
450 455 460

Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro
465 470 475 480

Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn
485 490 495

Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu
500 505 510

- 192 -

Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr
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Thr Ile Ile Ile Val Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val
530 535 540

Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser
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<213> Artificial Sequence

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gtagtgactc ctcaagatgg agagcacttg ttccgctgtg agcaaggcgt acctgagcgc 240

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tctcgtgaac aaggcgacac tcgttcccga tggactcgcg ggactcctgg ccaaccatgt 360

- 193 -

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- 194 -

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- 195 -

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<212> PRT
<213> Artificial Sequence

<220>
<223> RSV F Protein Variant

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<221> MISC_FEATURE

<222> (550)..(550)

<223> Xaa is any nucleotide

<400> 567

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Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
35 40 45

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
50 55 60

Lys Lys Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
65 70 75 80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
85 90 95

Met Gln Ser Thr Gln Ala Thr Asn Asn Lys Lys Arg Lys Arg Arg Phe
100 105 110

Leu Gly Phe Leu Leu Gly Val Gly Ser Ala Ile Ala Ser Gly Val Ala
115 120 125

- 197 -

Val Ser Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Lys Ser
130 135 140

Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val
145 150 155 160

Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp Lys
165 170 175

Gln Leu Leu Pro Ile Val Asn Lys Gln Ser Cys Ser Ile Ser Asn Ile
180 185 190

Glu Thr Val Ile Glu Phe Gln Gln Lys Asn Asn Arg Leu Leu Glu Ile
195 200 205

Thr Arg Glu Phe Ser Val Asn Ala Gly Val Thr Thr Pro Val Ser Thr
210 215 220

Tyr Met Leu Thr Asn Ser Glu Leu Leu Ser Leu Ile Asn Asp Met Pro
225 230 235 240

Ile Thr Asn Asp Gln Lys Lys Leu Met Ser Asn Asn Val Gln Ile Val
245 250 255

Arg Gln Gln Ser Tyr Ser Ile Met Ser Ile Ile Lys Glu Glu Val Leu
260 265 270

Ala Tyr Val Val Gln Leu Pro Leu Tyr Gly Val Ile Asp Thr Pro Cys

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275

280

285

Trp Lys Leu His Thr Ser Pro Leu Cys Thr Thr Asn Thr Lys Glu Gly
290 295 300

Ser Asn Ile Cys Leu Thr Arg Thr Asp Arg Gly Trp Tyr Cys Asp Asn
305 310 315 320

Ala Gly Ser Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys Val Gln
325 330 335

Ser Asn Arg Val Phe Cys Asp Thr Met Asn Ser Leu Thr Leu Pro Ser
340 345 350

Glu Val Asn Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr Asp Cys
355 360 365

Lys Ile Met Thr Ser Lys Thr Asp Val Ser Ser Ser Val Ile Thr Ser
370 375 380

Leu Gly Ala Ile Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr Ala Ser
385 390 395 400

Asn Lys Asn Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys Asp Tyr
405 410 415

Val Ser Asn Lys Gly Val Asp Thr Val Ser Val Gly Asn Thr Leu Tyr
420 425 430

- 199 -

Tyr Val Asn Lys Gln Glu Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro
435 440 445

Ile Ile Asn Phe Tyr Asp Pro Leu Val Phe Pro Ser Asp Glu Phe Asp
450 455 460

Ala Ser Ile Ser Gln Val Asn Glu Lys Ile Asn Gln Ser Leu Ala Phe
465 470 475 480

Ile Arg Lys Ser Asp Glu Leu Leu His Asn Val Asn Ala Gly Lys Ser
485 490 495

Thr Thr Asn Ile Met Ile Thr Thr Ile Ile Ile Val Ile Val Ile
500 505 510

Leu Leu Ser Leu Ile Ala Val Gly Leu Leu Leu Tyr Cys Lys Ala Arg
515 520 525

Ser Thr Pro Val Thr Leu Ser Lys Asp Gln Leu Ser Gly Ile Asn Asn
530 535 540

Ile Ala Phe Ser Asn Xaa
545 550

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<212> DNA
<213> Artificial Sequence

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<220>

<223> RSV F Protein Variant

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gtagtgactc ctcaagatgg agagcacttg ttccgctgtg agcaaggctt acctgagcgc 240

cctgaggacc ggttgtaca ccagcgtgat caccatcgag ctgagcaaca tcaagaagaa 300

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gttcgcacta gtggtagctc gactcggtgt agttcttctt caagtgcac ggcaccgacg 420

ccaaggtaaa gctgatcaag caagagctgg acaagtacaa gaacgccgtg accgagctgc 480

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gttctcgacc tgttcatgtt cttgcggcac tggctcgacg ttgacgacta cgtcagctga 600

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- 201 -

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- 202 -

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- 203 -

<210> 569
<211> 25
<212> PRT
<213> respiratory syncytial virus

<400> 569

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Ala Lys Lys Thr Asn Val Thr Leu Ser
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<210> 570
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<213> respiratory syncytial virus

<400> 570
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<210> 571
<211> 1725
<212> DNA
<213> respiratory syncytial virus

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- 204 -

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- 205 -

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<211> 1726
<212> DNA
<213> Artificial Sequence

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<223> RSV F Protein Variant

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- 206 -

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cagagccatcg catttattcg taaatccgtt gaattattac ataatgtaaa tgctggtaaa 1560
tccaccacaa atatcatgtt aactactata attatgtttttaat attgttataatc 1620

- 207 -

ttaattgctg ttggactggc tcttatactg taaggccaga agcacaccag tcacactaag 1680
caaagatcaa ctgagtggt aataataat tgcatttagt aactaa 1726

<210> 573
<211> 1722
<212> DNA
<213> Consensus Sequence

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agcaaaggct atcttagtgc tctgagaact ggttggata ccagtgttat aacatagaat 180
aagtaatatc aagaaaaata agtgaatgg aacagatgca aggtaaaatt gataaaacaa 240
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- 208 -

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<213> Synthetic

- 209 -

<400> 574

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU01/01517

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. 7: C07K 14/08, 14/115, 14/135, 16/10; A61K 38/16, 39/155; A61P 11/00; C12N 15/45, 15/40; C12Q 1/68; G01N 1/68;

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubMed, keywords: F protein, fusion, RSV, respiratory syncytial virus, Paramyxoviridae, Pneunovirus and similar terms; STN file Medline: fusion, RSV, and sequences RARR, KKRKRR; Espace, keywords, f protein, expression; ANGIS: seq id's 3, 4, 5, 6, 556, 559, 562

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 780475 B1 (SCHWEIZ SERUM- & IMPFINSTITUT) 25 June 1997 see whole document	1 - 14 1 - 25, 56 - 59
X, Y	WO 99/02694 A1 (THE UNIVERSITY OF QUEENSLAND) 21 January 1999 see whole document	1- 25, 56 -59
X, Y	WO 96/09378 A1 (THE GENERAL HOSPITAL CORPORATION) 28 March 1996 see whole document	1- 25, 56 -59

Further documents are listed in the continuation of Box C See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search <u>24 January 2002</u>	Date of mailing of the international search report <u>19 FEB 2002</u>
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer DAVID GRIFFITHS Telephone No : (02) 6283 2628

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU01/01517

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,619,942 A (TIDWELL, <i>et al.</i>) 28 October 1986 col. 1, line 61 - col. 2, line 16	26
X	WO 99/62932 A2 (VANDERBILT UNIVERSITY) 9 December 1999 page 12 line 15 to page 14 line 11	41, 62, 75, 79
X	SAKURAI, Hiroshi <i>et al.</i> , "Human Antibody Responses to Mature and Immature Forms of Viral Envelope in Respiratory Syncytial Virus Infection: Significance for Subunit Vaccines", Journal of Virology, Vol. 73, No. 4, April 1999, pp. 2956 - 2962 see whole document	41, 62, 75, 79
X	LI, Xiaomao <i>et al.</i> , "Protection against Respiratory Syncytial Virus Infection by DNA Immunization", J. Exp. Med., Vol 188, No. 4, 17 August 1998, pp. 681 - 688 see whole document	41, 62, 75, 79
X	LOPEZ, Juan A. <i>et al.</i> , "Antigenic Structure of Human Respiratory Syncytial Virus Fusion Protein", Journal of Virology, Vol. 72, No. 8, August 1998, pp. 6922-6928 see whole document	41, 62, 75, 79
P, X	ZIMMER, G. <i>et al.</i> , "Proteolytic Activation of Respiratory Syncytial Virus Fusion Protein". Journal of Biological Chemistry, Vol. 276, No. 34, pp. 31642-31650 see whole document	44 - 49

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01517

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos :
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos : 1 - 41 (in part), 42, 43, 44 -79 (in part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The breadth of the claims is such that a full, meaningful search is not possible on economic grounds. The search was therefore confined largely to the optimisation of expression in eukaryotes by replacing less-preferred codons by more preferred codons. A keyword search was done to cover the other claimed aspects but due to the breadth of the claims this cannot be regarded as complete. It was not technically feasible to search claims 42 and 43.

3. Claims Nos :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See supplemental sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

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Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

The following separate inventions have been identified:

- (i) a method of facilitating the production of viral protein (e.g. claim 1)
- (ii) a method of regulating the functional activity of viral F protein (e.g. claim 26)
- (iii) a method of detecting an agent capable of regulating the functional activity of viral F protein (e.g. claim 34)
- (iv) an agent capable of regulating the functional activity of viral F protein (e.g. claim 41)
- (v) a viral F protein variant (e.g. claim 44)
- (vi) a recombinant viral protein construct optimised for expression in a eukaryote (e.g. claim 60).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/01517

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
EP	780475	AU	68208/96	CA	2228956	EP	846181
		WO	9706270				
WO	99/02694	AU	81999/98	EP	1002091		
WO	96/09378	AU	35099/95	CA	2200342	EP	781329
		TR	960230	US	5786464	ZA	9507846
		US	5795737	CA	2231394	EP	851868
		WO	9711086				
US	4619942	US	4324794	US	4397863		
WO	99/62932	US	6315810	US	6299827	DE	19723599
		EP	882679	JP	11005069		
END OF ANNEX							